807034

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SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY

SP. Clvic

Cross-Reference to Related Applications

~~This application is a continuation-in-part to my earlier copending application Serial No. 265,785, filed May 21, 1981, which was a continuation-in-part of my application Serial No. 168,453, filed July 10, 1980, now abandoned. Both of~~ The said earlier applications are expressly incorporated by reference herein in their entireties and relied upon.

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Technical Field of the Invention

The invention relates to novel soft steroids having anti-inflammatory activity, pharmaceutical compositions containing said soft steroids, novel chemical intermediates useful in the preparation of the steroids, and methods of administering said steroids to mammals in the treatment of inflammation.

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Background Art

Successful predictions on a rational basis of the biological activity of compounds leading to new drugs are the main objective of drug designers. This has usually been achieved by considering a known bioactive molecule as the basis for structural modifications, either by the group or biofunctional moieties approach or by altering the overall physical-chemical properties of the molecule. Thus, the main aim has been to design, synthesize, and test new compounds structurally analogous to the basic bioactive molecule which have, however, improved therapeutic and/or pharmacokinetic properties. Although "vulnerable" moieties have been identified as the ones whose role is the bioinactivation or metabolic elimination of the drug after it has performed its role, little or no attention has been paid in the drug-design process to the rational design of the metabolic disposition of the drugs. This has been the case despite the fact that the toxicity of a number of bioactive molecules is due to their increased elimination half-life, stability, or other factors introduced during the design of increasing their activity. Drugs and particularly their metabolic processes contribute to the various toxic processes by formation of active

metabolites. The phenomenon of metabolic activation to reactive intermediates which covalently bind to tissue macromolecules is the initial step in cell damage. It is also clear that the most toxic metabolites will not survive long enough to be excreted and identified; thus, studies of the stable metabolites may provide misleading information.

It is clear that, in order to prevent and/or reduce toxicity problems related to drugs, the metabolic disposition of the drugs should be considered at an early stage of the drug-design process. This is true particularly when one considers that the body can attack and alter chemically quite stable structures and that, even if a drug is 95% excreted unchanged, the unaccounted small portion can, and most likely will, cause toxicity.

"Soft drugs" can be defined as biologically active chemical compounds (drugs) which might structurally resemble known active drugs (soft analogues) or could be entirely new types of structures, but which are all characterized by a predictable <u>in vivo</u> destruction (metabolism) to nontoxic moieties, after they achieve their therapeutic role. The metabolic disposition of the soft drugs takes place with a <u>controllable rate</u> in a predictable manner.

The present inventor has found five major classes of soft drugs. One of the most useful classes was termed the "inactive metabolite" approach which can be advantageously employed to design especially valuable "soft drugs". This approach starts with a known inactive metabolite of a drug or a drug class; followed by modifying the metabolite to resemble structurally (isosteric and/or isoelectronic) the active drug (i.e., activation); and designing the metabolism of the activated species to lead to the starting inactive metabolite after achieving the desired therapeutic role, without the formation of toxic intermediates (i.e.,

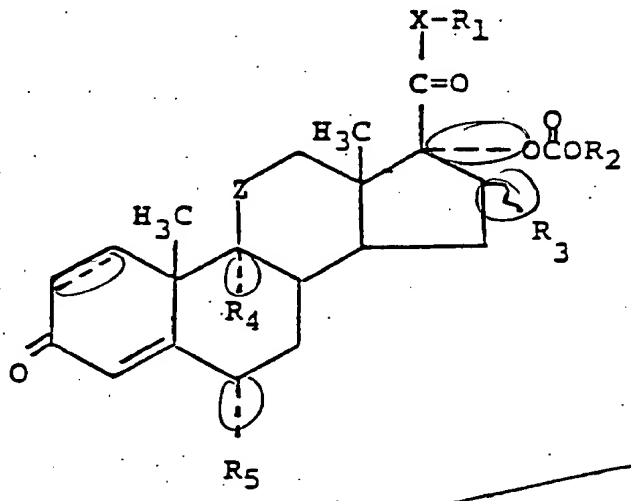
predictable metabolism). The "inactive metabolite" approach further allows controlling the rate of metabolism and pharmacokinetic properties by molecular manipulation in the activation stage. Also, if no useful inactive metabolite is known, one can be designed by the introduction of transporting groups in noncritical structural parts.

Summary of the Invention

The present inventor has now applied his inactive metabolite approach to the case of the natural and synthetic glucocorticosteroids and has designed the soft steroidal anti-inflammatory agents of the present invention, beginning with the known inactive natural metabolites of the glucocorticosteroids. Thus, for example, in the case of hydrocortisone, one of its major, inactive metabolites, cortienic acid, i.e., 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid, has been used as a starting point and activated by the introduction of suitable non-toxic 17α - and 17β -substituents, which activated derivatives will cleave in vivo, after accomplishment of their therapeutic role, to the starting inactive metabolite and other nontoxic moieties.

In accord with the foregoing, the present invention provides novel soft steroids having anti-inflammatory activity, said steroids having the structural formula

T0060X



(I)

PS

wherein: PS

PO R_1 is C_{1-10} alkyl; C_{2-10} (monohydroxy or polyhydroxy)alkyl; C_{1-10} (monohalo or polyhalo)alkyl; or $-CH_2COOR_6$ wherein R_6 is unsubstituted or substituted C_{1-10} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl or C_{2-10} alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, T0060X $-NHC(=O)-(C_1-C_{10}$ alkyl) and $-OC(=O)-(C_1-C_{10}$ alkyl), PO+10 or R_6 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxycarbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl; or R_1 is $-CH_2CONR_7R_8$ wherein R_7 and R_8, which can be the same or different, are each hydrogen, lower alkyl, C_{3-8} cycloalkyl, phenyl or benzyl, or R_7 and R_8 are combined such that $-NR_7R_8$ represents the residue of a saturated monocyclic secondary amine; or R_1 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group of phenyl and benzyl substituents defined hereinabove with respect to R_6; or R_1 is

$-\underset{R_9}{\overset{|}{C}}H-Y-$(lower alkyl) wherein Y is $-S-$, $-SO-$, $-SO_2-$ or $-O-$ and R_9 is hydrogen, lower alkyl or phenyl, or R_9 and the lower alkyl group adjacent to Y are combined so that R_1 is a cyclic system of the type $-\underset{\text{alkylene}}{\overset{Y}{\overset{|}{C}}}H-$ wherein Y is defined as above and the alkylene group contains 3 to 10 carbon atoms, of which at least 3 and no more than 6 are ring atoms; or R_1 is $-\underset{R_{10}}{\overset{|}{C}}H-OCR_6$ wherein R_6 is defined as hereinabove and R_{10} is hydrogen, lower alkyl, phenyl or haloalkyl;

R_2 is unsubstituted or substituted C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl or C_2-C_{10} alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, $-NHC-$(lower alkyl) and $-OC-$(lower alkyl), or R_2 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxycarbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl;

R_3 is hydrogen, α-hydroxy, β-hydroxy, α-methyl, β-methyl, $=CH_2$, or α- or β-$OCOR_2$ wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen, fluoro or chloro;

R_5 is hydrogen, fluoro, chloro or methyl;

X is $-O-$ or $-S-$;

Z is carbonyl or β-hydroxymethylene;

and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated.

A group of preferred compounds of formula (I) consists of those wherein:

R_1 is C_1-C_6 alkyl; C_1-C_6 (monohalo or polyhalo)-alkyl; $-CH_2COOR_6$ wherein R_6 is C_1-C_6 alkyl; $-CH_2-Y-(C_1$-C_6 alkyl) wherein Y is $-S-$, $-SO-$, $-SO_2-$ or $-O-$; or $-CH_2-OCR_6'$ wherein R_6' is C_1-C_6 alkyl or phenyl;

R_2 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl;

R_3 is hydrogen, α-hydroxy, α-methyl, β-methyl or α-$OCOR_2$ wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen or fluoro;

R_5 is hydrogen or fluoro;

Z is β-hydroxymethylene;

and X and the dotted line in ring A are defined as hereinabove.

The invention further provides anti-inflammatory quaternary ammonium salts of selected compounds of formula (I), as discussed in further detail below. Novel intermediates to the compounds of formula (I), e.g, the corresponding compounds wherein R_1 is hydrogen, are provided also.

The soft steroids of formula (I) and quaternary ammonium salts thereof are extremely potent local anti-inflammatory agents; however, by virtue of the fact that their facile <u>in vivo</u> destruction leads only to the inactive steroidal metabolite, the present compounds have far less systemic activity than the known glucocorticosteroids from whose inactive metabolites they are derived. Indeed, many of the compounds of the present invention are entirely devoid of systemic activity. Such minimal or non-existent systemic activity means that the compounds of the present invention can be used in the local (e.g., topical) treatment of inflammatory conditions without the serious

systemic side effects which attend use of the known glucocorticosteroids.

Detailed Description of the Invention and the Preferred Embodiments:

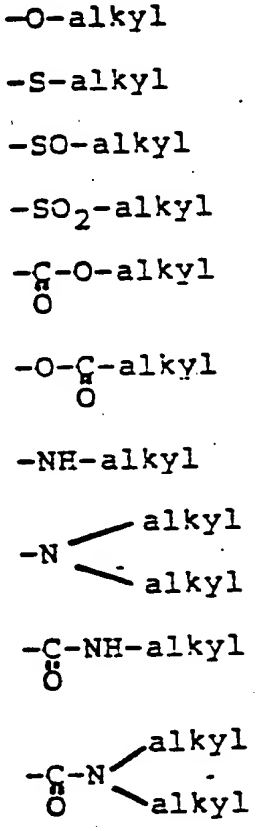
With respect to the various groups encompassed by the generic terms used here and throughout this specification, the following definitions and explanations are applicable:

The alkyl, alkenyl and alkylene groupings can be straight or branched-chain groups containing the aforementioned number of carbon atoms. Likewise, the alkyl portions of the alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, alkanoyloxy, haloalkyl, monoalkylamino, dialkylamino, monoalkylcarbamoyl and dialkylcarbamoyl groupings each can be straight or branched-chain. The term "lower" used in conjunction with any of those groupings or in conjunction with "alkyl" is intended to indicate that each alkyl portion therein can contain 1 to 8 carbon atoms.

Specific examples of alkyl radicals encompassed by formula (I), whether as specific values for R_1 or R_2, or as a portion of a R_1, R_2, or R_3 group, include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl and their branched-chain isomers, as well as their straight and branched-chain higher homologues in the instances where "alkyl" can contain more than 8 carbon atoms. The alkenyl radicals can be exemplified by vinyl, propenyl and butenyl. Illustrative of the cycloalkyl and cycloalkenyl radicals are cyclopentyl, cyclohexyl, cyclopentenyl and cyclohexenyl. The alkylene moieties are typified by trimethylene, tetramethylene and the like.

The alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, alkanoyloxy, monoalkylamino, dialkylamino, monoalkylcarbamoyl and dialkylcarbamoyl

groupings are of the type



respectively, wherein alkyl is as hereinbefore defined and exemplified.

With respect to the structural variables encompassed by the group of preferred compounds of formula (I) identified hereinabove, the term "C_{1-4}-C_6 alkyl" is used to refer to a straight or branched-chain alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl and the like. In addition, the term "C_{1-4}-C_6 (monohalo or polyhalo)alkyl" is used to refer to a straight or branched-chain alkyl group having 1 to 6 carbon atoms substituted with from 1 to 3 halogen atoms, the term "halogen" as used herein including a chlorine atom, a bromine atom, an iodine atom or a fluorine atom. Specific examples of the contemplated

monchaloalkyl and polyhaloalkyl groups include chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1-chloroethyl, 2-chloroethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 1,2-dichloroethyl, 1-chloropropyl, 3-chloropropyl, 1-chlorobutyl, 1-chloropentyl, 1-chlorohexyl, 4-chlorobutyl and the like. Also, the term "C_3-C_8 cycloalkyl" is used to refer to a cycloalkyl radical having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

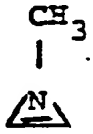
When R_1 in formula (I) is $-CH_2CONR_7R_8$ wherein $-NR_7R_8$ represents the residue of a saturated monocyclic secondary amine, such monocycles preferably have 5 to 7 ring atoms optionally containing another hetero atom (-O-, -S- or -N-) in addition to the indicated nitrogen atom, and optionally bear one or more substituents such as phenyl, benzyl and methyl. Illustrative of residues of saturated monocyclic secondary amines which are encompassed by the $-NR_7R_8$ term are morpholino, 1-pyrrolidinyl, 4-benzyl-1-piperazinyl, perhydro-1,2,4-oxathiazin-4-yl, 1- or 4-piperazinyl, 4-methyl-1-piperazinyl, piperidino, hexamethyleneimino, 4-phenylpiperidino, 2-methyl-1-pyrazolidinyl, 1- or 2-pyrazolidinyl, 3-methyl-1-imidazolidinyl, 1- or 3-imidazolidinyl, 4-benzylpiperidino and 4-phenyl-1-piperazinyl.

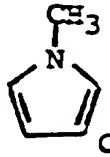
Selected compounds of formula (I), i.e. compounds wherein R_1 is α-haloalkyl, readily form the corresponding soft quaternary ammonium salts which are likewise useful as soft anti-inflammatory agents. Thus, for example, the selected haloalkyl derivative of formula (I) can simply be reacted with a tertiary amine (≡N) or an unsaturated amine (>N) to afford the corresponding quaternary ammonium salt. The reactants are

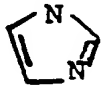
generally used in approximately equimolecular proportions and the reaction is conducted in the presence of an inert solvent (e.g., ether, acetonitrile, CH_2Cl_2 or the like), at a temperature of from room temperature to the reflux temperature of the solvent, for approximately 2 to 24 hours. Alternatively, the reaction can be conducted in the absence of a solvent by mixing the two reactants together and maintaining them at room temperature or between 20° to 70°C for 2 to 24 hours. In either case, the crystalline salt formed can be purified by crystallization from an ether-ethanol mixture, or the like.

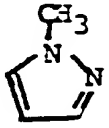
The expression "unsaturated amine" used above denotes N-heterocyclic unsaturated systems having 3 to 10 members in the ring, and substituted derivatives thereof, where the unsaturation corresponds to the maximum number of non-cumulative double bonds, provided that the nitrogen atom contains no hydrogen atom as a substituent. The following examples will sufficiently illustrate the scope of the defined term:

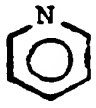
TO120X

1-Methylazirine 

1-Methylpyrrole 

1-Methylimidazole 

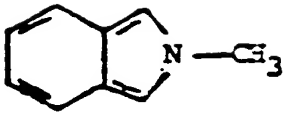
1-Methylpyrazole 

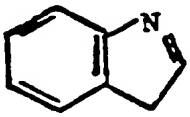
Pyridine 

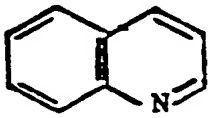
Pyrazine 

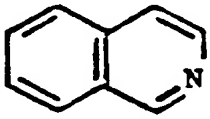
Pyrimidine 

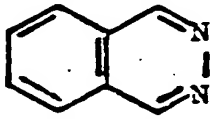
Pyridazine 

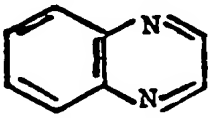
2-Methylisoindole 

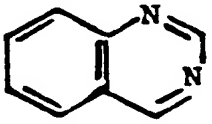
3E-indole 

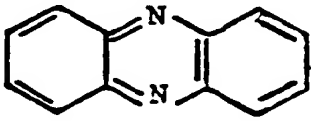
Quinoline 

Isoquinoline 

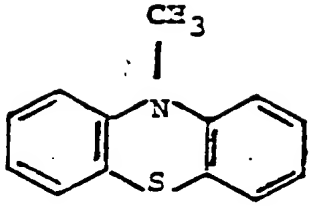
Phthalazine 

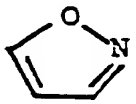
Quinoxaline 

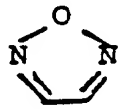
Quinazoline 

Phenazine 

Isothiazole 

10-Methylphenothiazine 

Isoxazole 

Furazan 

Substituted derivatives of the unsaturated amines include groups as shown above containing one or more alkyl, -COO(alkyl) or -OCO(alkyl) substituents.

With respect to the expression "tertiary amine", this expression denotes amines wherein the nitrogen atom has no hydrogen atoms attached thereto and which are not among the N-heterocyclic unsaturated systems encompassed by the expression "unsaturated amine" as defined above. Typically, the term "tertiary amine" includes trialkylamines, wherein the alkyl groups, which can be the same or different, each preferably contain 1 to 8 carbon atoms; trialkoxyamines wherein the alkoxy portions each contain 1 to 8 carbon atoms; tertiary saturated cyclic amines such as quinuclidine or substituted quinuclidine (e.g., 3-acetoxyquinuclidine); and N-substituted derivatives of secondary saturated cyclic amines [e.g., an N-substituted derivative of morpholine, pyrrolidine, imidazolidine, pyrazolidine, piperidine or piperazine, wherein the N-substituent can be a group such as (C_1-C_8)alkyl], optionally containing additional substituents such as methyl.

Preferred quaternary ammonium salts include those derived from 1,2-dimethylpyrrolidine, 3-acetoxyquinuclidine, 1-methylpyrrolidine, triethylamine

and N-methylimidazole. Especially preferred are the quaternary ammonium salts derived from the reaction of the aforesaid amines with compounds of formula (I) wherein Z is β-hydroxymethylene and R_1 is chloromethyl, most especially when R_2 is lower alkyl.

While all of the compounds encompassed by formula (I) above essentially satisfy the objectives of the present invention, nevertheless certain groups of compounds remain preferred. A "first" group of preferred compounds of formula (I) has been set forth in the Summary of the Invention hereinabove.

Another preferred group of compounds consists of the compounds of formula (I) wherein Z, X, R_1 and R_2 are defined as hereinabove, and the remainder of the structural variations are identical to those of hydrocortisone (i.e., R_3, R_4 and R_5 are each a hydrogen atom and the 1,2-linkage is saturated) or of prednisolone (i.e., R_3, R_4 and R_5 are each a hydrogen atom and the 1,2-linkage is unsaturated), most especially when R_1 and R_2 are as defined with respect to the "first" group of preferred compounds set forth hereinabove.

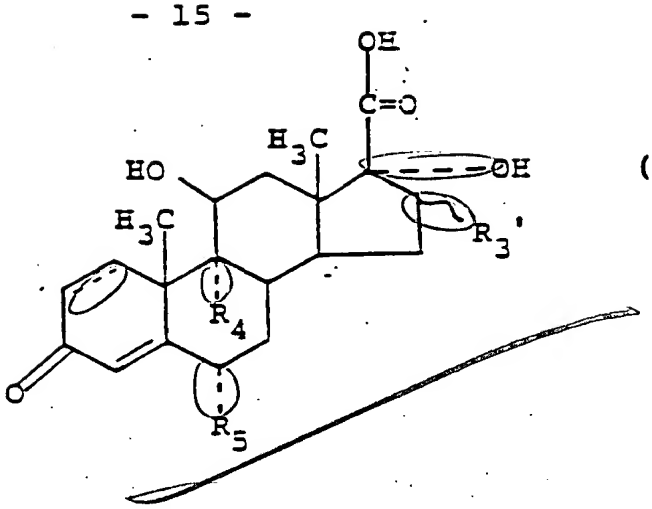
Another preferred group of compounds consists of the 6α- and/or 9α-fluoro and 16α- or 16β-methyl congeners of the compounds indicated in the preceding paragraph. Within this group, the compounds wherein Z, X, R_1 and R_2 are defined as hereinabove and the remaining structural variables are identical to those of fludrocortisone, betamethasone and dexamethasone are particularly preferred, most especially when R_1 and R_2 are as defined with respect to the "first" group of preferred compounds set forth hereinabove. Other compounds of particular interest within this group are those wherein Z, X, R_1 and R_2 are defined as hereinabove and the remaining structural variables are identical to those of triamcinolone, flumethasone, fluprednisolone or paramethasone, particularly when R_1 and R_2 are as defined

with respect to the "first" group of preferred compounds set forth hereinabove. Yet other interesting compounds are those wherein Z, X, R_1 and R_2 are defined as hereinabove, R_3 is α-$OCOR_2$, and the remaining structural variables are identical to those of triamcinolone, particularly when R_1 and R_2 are as defined with respect to the "first" group of preferred compounds set forth hereinabove.

In each of the groups of compounds indicated in the three preceding paragraphs, the compounds wherein X is oxygen are particularly preferred. Most especially preferred are the compounds encompassed by the groups indicated above wherein Z is β-hydroxymethylene, wherein X is oxygen, wherein R_2 is C_1-C_6 alkyl (particularly methyl, ethyl, propyl or isopropyl), and wherein R_1 is C_1-C_6 alkyl, C_1-C_6 (monohalo)alkyl (particularly chloromethyl) or -CH_2-Y-(C_1-C_6 alkyl) wherein Y is defined as hereinabove (particularly when the C_1-C_6 alkyl group is methyl).

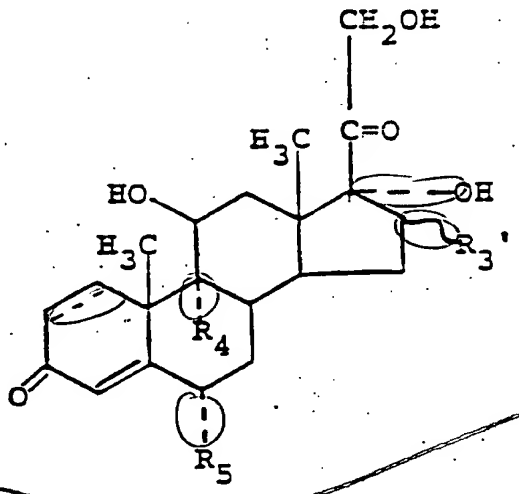
The compounds of formula (I) can generally be prepared by known methods, the method of choice being dependent on the identity of the various substituents in the desired final product.

One generally useful method for the preparation of the compounds of formula (I) wherein Z is β-hydroxymethylene and X is oxygen utilizes steroidal starting materials of the formula



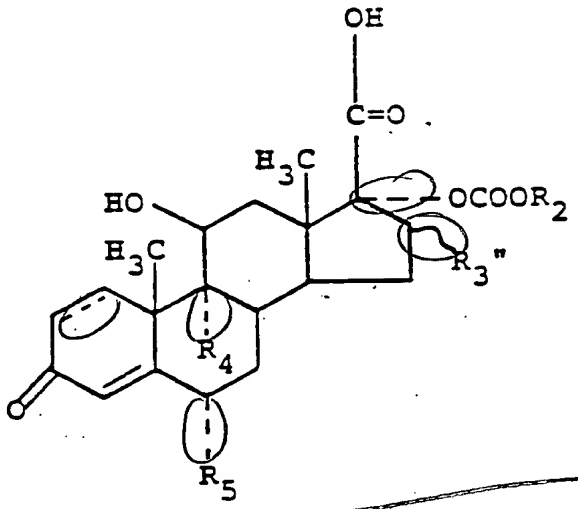
(II)

wherein R_4, R_5 and the dotted line in ring A are defined as before and R_3' is hydrogen, α-methyl, β-methyl, α-OH, β-OH or $=CH_2$ (and which can be conveniently prepared by treatment of the corresponding 21-hydroxypregnenolones of the formula



wherein R_4, R_5, R_3' and the dotted line in ring A are defined as above with $NaIO_4$ in a suitable organic solvent at room or elevated temperature.) According to this process of the invention, a starting material of formula (II) is reacted with R_2OCOCl or R_2OCOBr (formed by reacting R_2OH with $COCl_2$ or $COBr_2$, wherein R_2 is defined as above), under anhydrous conditions, in an appropriate inert organic solvent such

as dichloromethane, chloroform or tetrahydrofuran, preferably in the presence of a suitable acid acceptor (e.g., triethylamine, pyridine, calcium carbonate or other appropriate base). Time and temperature are not critical factors; however, the reaction is conveniently carried out at a temperature between 0°C and room temperature, for about 1 to 6 hours. The resultant novel 17β-carboxylic acid 17α-carbonate has the formula

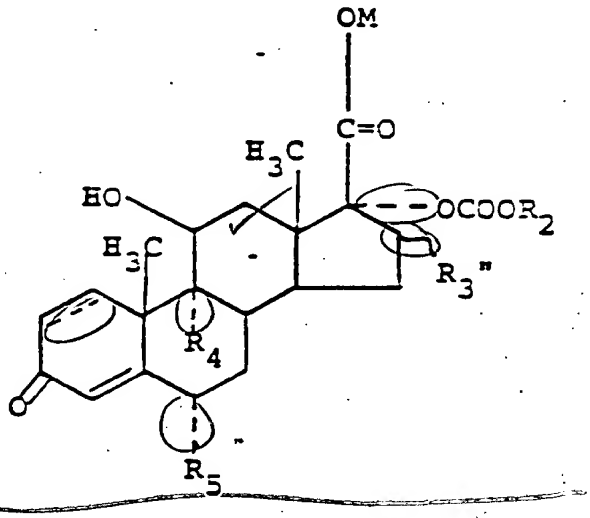


(III)

wherein R_2, R_4, R_5 and the dotted line in the A ring are defined as above and R_3" is H, α-CH_3, β-CH_3, α-$OCOOR_2$, β-$OCOOR_2$ or $=CH_2$. When R_3' in the starting material of formula (II) is α-OH or β-OH, sufficient R_2OCOCl or R_2OCOBr is generally employed to ensure formation of the carbonate grouping at the 16-position as well as at the 17-position [i.e., when R_3' in formula (II) is OH, R_3" in the resultant intermediate of formula (III) is α- or β-$OCOOR_2$].

Sometimes, when a compound of formula (I) wherein R_2 contains a sulfinyl or sulfonyl grouping is desired, such a grouping is not introduced via the R_2OCOCl/R_2OCOBr reaction, but is prepared from the corresponding thio-containing R_2 derivative at a later stage in the synthetic scheme, as will be discussed in more detail below.

After the above-described introduction of the 17α-substituent, the resultant novel intermediate of formula (III) is converted to its corresponding metal salt of the formula



(IV)

wherein R_2, R_3", R_4, R_5 and the dotted line in the ring A are defined as above, and M is a suitable metal, e.g. alkali metal (such as sodium or potassium), alkaline earth metal/2, or thallium or NH_4^+. The novel salt of formula (IV) is typically formed by reacting the steroid of formula (III) with a hydroxide (MOH) or alkoxide (MOR) in an appropriate organic solvent, such as ethyl ether or tetrahydrofuran, at a temperature of 0°C to room temperature, for 0.5 to 4 hours. Then, the salt of formula (IV) is reacted with a compound of the formula R_1-W wherein R_1 is defined as hereinabove and W is halogen, to afford the desired final product of formula (I). This step of the reaction sequence can be conveniently conducted at room temperature for about 1 to 24 hours, or at the boiling of the solvent (i.e. acetonitrile, THF, etc.) When it is desired to introduce a halo-substituted R_1 grouping into the steroid, e.g., when a compound of formula (I) wherein R_1 is chloromethyl is desired, it has been found that the reaction proceeds well using hexamethylphosphoramide as

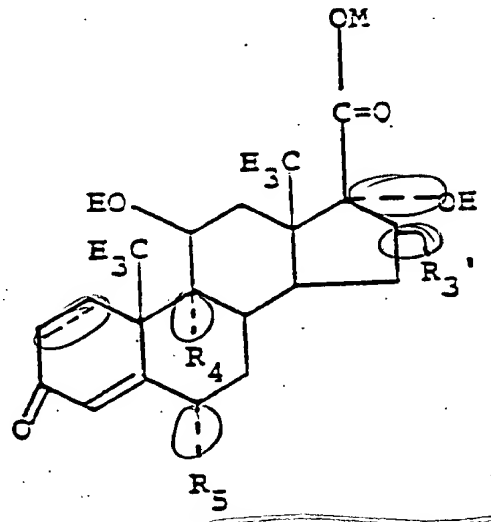
the solvent at lower temperatures (0-10°C) and employing a R_1-W reactant wherein W is iodine (e.g., iodochloromethane). When a non-halogen containing R_1 grouping is desired (e.g., R_1 = alkyl or $-CH_2COOR_6$ where R_6 is alkyl, etc.), no such restrictions need be placed on the R_1-W reactant or on the solvent; thus, W can be any halogen, preferably chloro or bromo, and the usual organic solvents such as dimethylformamide, dichloromethane, acetonitrile, tetrahydrofuran or chloroform can, if desired, be used instead of hexamethylphosphoramide. When a compound of formula (I) wherein R_1 contains a sulfinyl or sulfonyl grouping is desired, such a grouping is not generally introduced via the R_1-W reaction, but is subsequently prepared from the corresponding thio steroid, as described below.

The compounds of formula (I) wherein R_1 (or R_2) is a sulfinyl- or sulfonyl-containing grouping can be prepared by oxidation of the corresponding thio steroids. Thus, for example, a compound of formula (I) wherein R_1 is $-\underset{R_9}{CH}-S-$(lower alkyl) [wherein R_9 is H, lower alkyl, or combined with the lower alkyl group adjacent to S to form a cyclic system, as described hereinabove] can be reacted with 1 equivalent of m-chloroperoxybenzoic acid at 0°-25°C for 1 to 24 hours, in a suitable solvent such as chloroform, to afford the corresponding compound of formula (I) wherein R_1 is $-\underset{R_9}{CH}-SO-$(lower alkyl), or with 2 equivalents of m-chloroperoxybenzoic acid to afford the corresponding compound of formula (I) wherein R_1 is $-\underset{R_9}{CH}-SO_2-$(lower alkyl). This type of reaction can also be utilized to prepare compounds of formula (I) wherein R_1 is $-CH_2COOR_6$ wherein R_6 is substituted alkyl, cycloalkyl, cycloalkenyl, alkenyl, phenyl, or benzyl, wherein the substituent is lower alkylsulfinyl or lower alkylsulfonyl, from the corresponding lower alkylthio-substituted formula (I) steroids; to prepare compounds of formula (I) wherein

R_1 is lower alkylsulfinyl- or alkylsulfonyl- substituted phenyl or benzyl from the corresponding lower alkylthio-substituted formula (I) steroids; and to prepare compounds of formula (I) wherein R_2 is substituted alkyl, cycloalkyl, cycloalkenyl, alkenyl, phenyl or benzyl wherein the substituent is lower alkylsulfinyl or lower alkylsulfonyl, from the corresponding lower alkylthio-substituted formula (I) steroids.

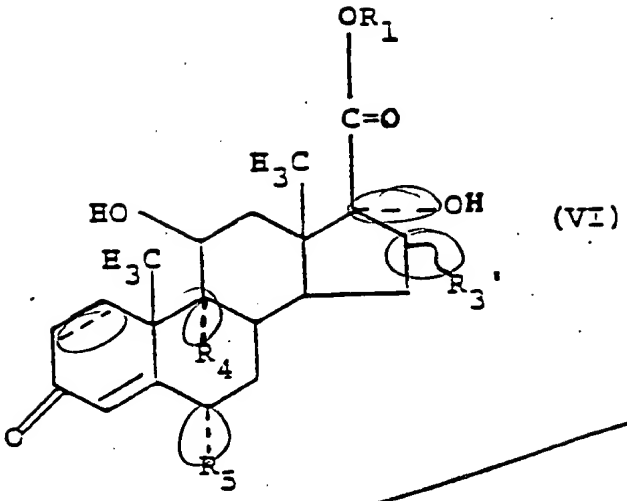
When the compounds of formula (I) wherein R_3 is α- or β-hydroxy are desired, same can be prepared by partial acid hydrolysis of the corresponding compounds of formula (I) wherein R_3 is α- or β-$OCOOR_2$, in a suitable solvent medium. Use of a mild reagent, e.g., oxalic acid in methanol, is desirable. Alternatively, hydrolysis of the 16-carbonate to the 16-hydroxy compound could be carried out at an earlier stage in any synthetic scheme described herein after the introduction of the 16,17-carbonate groupings, e.g., selective hydrolysis of an intermediate of formula (III) having 16 and 17 carbonate groupings to the corresponding 16-hydroxy 17-carbonate, followed by conversion to the corresponding compound of formula (I) as described supra.

Another process for the preparation of the compounds of formula (I) wherein Z is β-hydroxymethylene and X is oxygen utilizes the same 17α-hydroxy-17β-carboxylic acid starting materials of formula (II) as are employed in the synthetic scheme described supra, but involves formation of the 17 β-$COOR_1$ grouping prior to, rather than after, introduction of the 17α-$OCOOR_2$ substituent. Essentially, the same non-steroidal reactants, reaction conditions, etc., as described above are used for the introduction of each group. Thus, the starting material of formula (II) is first reacted with MOH or MOR to form the corresponding intermediate of the formula



(V)

wherein R_3', R_4, R_5 and M and the dotted line in ring A are defined as above, which is then reacted with R_1W wherein R_1 and W are defined as above, to afford the corresponding 17β-carboxylate of the formula

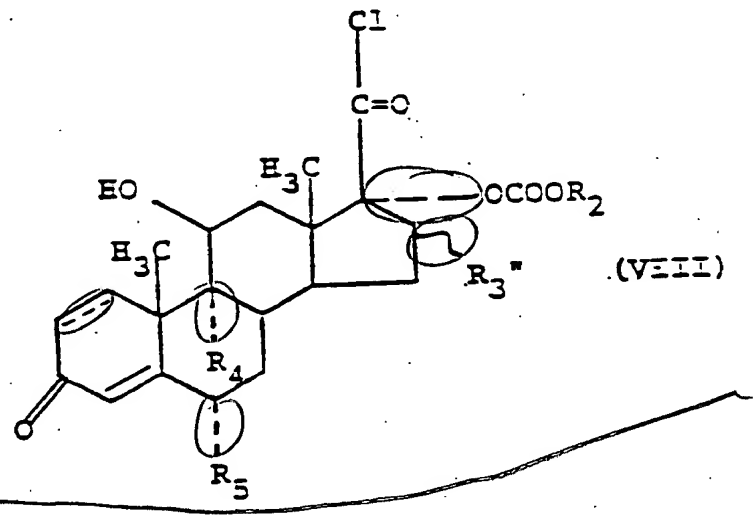


(VI)

wherein R_1, R_3', R_4, R_5 and the dotted line in ring A are defined as above, which is in turn reacted with R_2OCOCl or R_2OCOBr wherein R_2 is defined as above, to afford the corresponding 17α-carbonate of formula (I). The various parameters of the process of converting (II) to (V) are the same as those discussed in detail above with respect to the conversion of (III) to (IV). Likewise, the process parameters for converting (V) to (VI) parallel those detailed above with respect to converting (IV) to (I). Similarly, the process parameters for converting (VI) to (I) are basically the same as those given above for the conversion of (II) to (III). Thus, again, when the starting material contains a 16-hydroxy group, the 16,17-dicarbonate of formula (I) will be formed which can then be selectively hydrolyzed, if desired, to the corresponding 16-hydroxy-17-carbonate of formula (I). And, again, the compounds of formula (I) in which R_1 or R_2 is a sulfinyl- or sulfonyl-containing grouping can be conveniently prepared by oxidation of the corresponding thio-containing compounds of formula (I) as detailed hereinabove. Alternatively, the compounds of formula (I) wherein R_1 is a sulfinyl- or sulfonyl-containing group [e.g., when R_1 is $-\underset{R_9}{\underset{|}{CH}}-SO-$(lower alkyl) or $-\underset{R_9}{\underset{|}{CH}}-SO_2-$(lower alkyl)] can be prepared

by oxidation, preferably with m-chloroperoxybenzoic acid, of the corresponding compounds of formula (VI) in which R_1 is a thio-containing group, followed by introduction of the 17α-$OCOOR_2$ substituent to the resultant sulfinyl or sulfonyl compound.

Another possible process for the preparation of the compounds of the present invention, which can be used to prepare compounds of formula (I) wherein Z is β-hydroxymethylene and X is oxygen or sulfur, utilizes the 17β-carboxylic acid 17α-carbonate intermediates of formula (III) above. According to this process, an intermediate of formula (III) is successively treated, first with a mild acyl chloride forming agent, e.g. such as diethylchlorophosphate or oxalyl chloride, to form the corresponding novel acid chloride of the formula

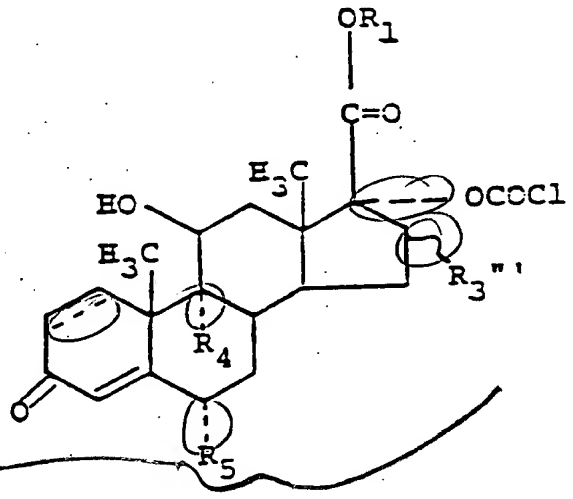


(VIII)

wherein R_2, R_3", R_4, R_5 and the dotted line in ring A are defined as above, and then with R_1XM' wherein R_1 and X are defined as before, and M' is hydrogen or M (M is defined as above), in an inert solvent (e.g., $CHCl_3$, THF, acetonitrile or DMF), at a temperature between about 0°C and the boiling point of the solvent, for 1 to 6 hours, to afford the corresponding compound of formula (I). When using a compound of the formula R_1XM' wherein M' is hydrogen, an acid scavenger

such as triethylamine is preferably present in the reaction system. The two steps of this process can be very conveniently run in the same solvent, without isolating the acid chloride of formula (VIII) formed in the first step. This process is of particular value when a compound of formula (I) wherein X is S is desired.

Yet another desirable process for the preparation of the compounds of formula (I) wherein Z is β-hydroxymethylene and X is oxygen utilizes the 17 α-hydroxy-17β carboxylates of formula (VI) above. According to this process, an intermediate of formula (VI) is reacted with phosgene, in a suitable organic solvent (e.g., toluene, benzene, CH_2Cl_2 or acetonitrile) at a low temperature (-20°C to room temperature, e.g., 0°C), for about 2 hours (or until the reaction is complete). Evaporation to remove solvent and excess phosgene affords the desired novel 17α-chlorocarbonyloxy-17β-carboxylate intermediate of the formula

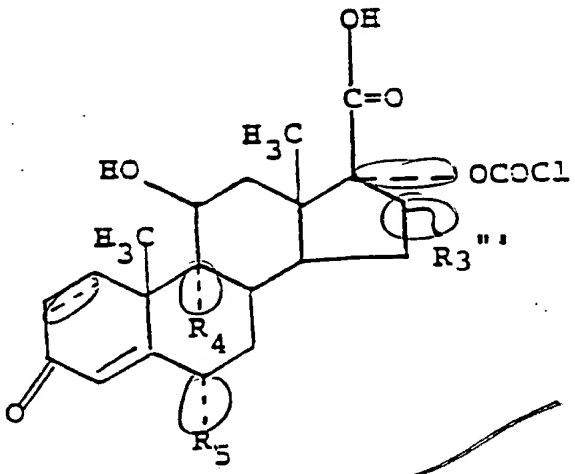


(VII)

wherein R_1, R_4, R_5 and the dotted line in ring A are defined as above, R_3"' is hydrogen, α-methyl, β-methyl, α-OCOCl, β-OCOCl or $=CH_2$. When R_3' in the starting material of formula (VI) is hydroxy, sufficient phosgene is generally employed to ensure formation of the chlorocarbonyloxy grouping at the 16-position as well as the 17-position [i.e., when

R_3' in formula (VI) is α-OH or β-OH, R_3''' in the resultant intermediate of formula (VII) is α- or β-OCOCl]. The intermediate of formula (VII) is then reacted with a compound of the formula R_2OM' wherein R_2 and M' are defined as above, in an inert solvent, preferably in the presence of an acid scavenger (e.g. triethylamine), to afford the corresponding compound of formula (I). When R_2OM' is an alcohol of the formula R_2OH, the reaction is conducted under the same conditions as in the reaction for conversion of compound (II) to compound (III). On the other hand, if a compound of the formula R_2OM is employed as R_2OM', the reaction conditions are described as above for conversion of compound (VIII) to compound (I). When R_3''' in the formula (VII) is OCOCl, sufficient R_2OM' is generally utilized to ensure conversion of both the 16- and 17α-substituents to $OCOOR_2$ groupings in the final product. And, again, the 16-hydroxy and the sulfinyl- and sulfonyl- containing compounds of formula (I) are most conveniently formed as a final step in the synthetic scheme.

As a variation of the process described immediately above, a steroidal 17α-hydroxy-17β-carboxylic acid starting material of formula (II) can be reacted with phosgene as described above, to afford the 17α-chlorocarbonyloxy-17β-carboxylic acid intermediate of the formula



(X)

wherein R_3''', R_4, R_5 and the dotted line in ring A are defined as above, which can then be reacted with R_2OM' as described supra, to afford the corresponding compound of formula (III) above. The novel intermediate can then be converted to a corresponding compound of formula (I) as described supra. Once again, the 16-hydroxy and the sulfinyl and sulfonyl derivatives are best prepared as a final step.

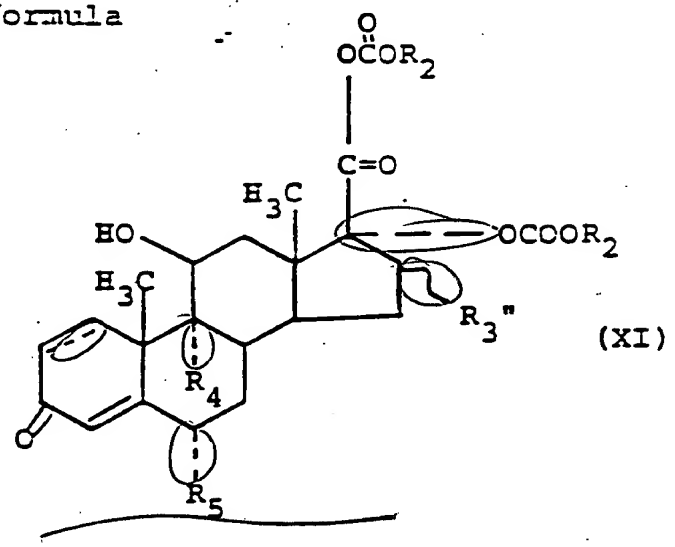
Still another process for the preparation of the compounds of formula (I) wherein Z is β-hydroxymethylene and X is oxygen utilizes the 17α-hydroxy-17β-carboxylates of formula (VI) above. In accord with this method, an intermediate of formula (VI) is reacted with an excess amount of a carbonate of the formula R_2OCOR_2 (which can be conveniently prepared by reacting phosgene with 2 equivalents of R_2OH) in the presence of an acid catalyst, to afford the corresponding compound of formula (I). Depending on the nature of the R_2 grouping, the R_2OCOR_2 reactant can also act as the solvent at the boiling point of the carbonate reactant, or at the boiling point of the corresponding R_2OH (which can conveniently be removed in this way from the reaction mixture, driving the reaction to completion), or the reactants can be combined in an appropriate inert organic solvent (e.g., an aromatic such as benzene or toluene, or a halogenated hydrocarbon such as dichloromethane or chloroform). And, again, the 16-hydroxy and the sulfinyl and sulfonyl compounds of formula (I) can conveniently be prepared as a final step in the process, although the intermediate of formula (VI) in which R_1 contains a sulfur atom could be first oxidized, and the resultant sulfinyl or sulfonyl compound of formula (VI) then reacted with R_2OCOR_2.

Other procedures for the preparation of selected compounds of formula (I) will be apparent to those skilled in the art. By way of example, a compound of formula (I) wherein R_1 or R_2 is halo-substituted can be subjected to a halogen exchange reaction in order to replace the halogen with a different halogen according to the order of reactivity Cl<Br<I. For example, reacting a chloroalkyl 17β-carboxylate of formula (I) with an alkali metal iodide, e.g., sodium iodide, will afford the corresponding iodoalkyl 17β-carboxylate. Similarly, a bromide salt (e.g., lithium bromide) can be reacted with a chloroalkyl 17β-carboxylate to give the corresponding bromoalkyl 17β-carboxylate. A suitable solvent for either reaction may be selected from the group consisting of hexamethylphosphoramide, acetone, ethanol, methyl ethyl ketone, dimethylacetamide, dimethylformamide and acetonitrile.

In like manner, a halogen exchange reaction based on relative solubilities can be used to convert a chloroalkyl 17β-carboxylate or an iodoalkyl 17β-carboxylate of formula (I) to the corresponding fluoroalkyl derivative. Silver fluoride can be employed in this reaction, which is conducted in a suitable organic solvent (e.g., acetonitrile), and which is especially useful in the preparation of the compounds in which R_1 is fluoromethyl or fluoroethyl.

The 21-hydroxypregnenolones from which the steroidal starting materials of formula (II) are prepared can be obtained commercially or prepared by known methods. Likewise, the non-steroidal starting materials used in the various processes discussed above are commercially available or can be prepared by known chemical procedures.

Also, a starting material of formula (II) above can be reacted with a compound of the formula R_2OCOCl or R_2OCOBr wherein R_2 is as defined above, to afford an intermediate of the formula

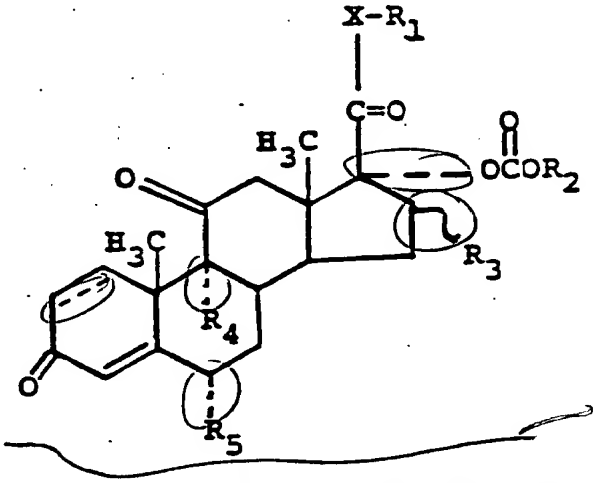


(XI)

wherein R_2, $R_3"$, R_4, R_5 and the dotted line in ring A are defined as above, which can be converted to the corresponding intermediate of formula (III) above by partial hydrolysis, with or without isolation of the compound of formula (XI). This reaction of a starting material of formula (II) with R_2OCOCl or R_2OCOBr can be carried out under the same conditions as the reaction of a compound of formula (II) with R_2OCOCl or R_2OCOBr as described hereinabove, except that R_2OCOCl or R_2OCOBr is used in an amount of 2 moles or more to one mole of the compound of the formula (II). The partial hydrolysis of the resultant compound of the formula (XI) can be carried out in an inert solvent in the presence of a catalyst. Examples of suitable catalysts include tertiary alkyl amines such as triethylamine, trimethylamine or the like; aromatic amines such as pyridine, 4,4-dimethylamino-pyridine, quinoline or the like; secondary alkyl amines such as diethylamine, dimethylamine or the like; and

inorganic bases such as sodium hydroxide, potassium hydroxide, potassium bicarbonate, or the like. Preferably, pyridine and potassium bicarbonate are employed. Examples of suitable inert solvents for use in the hydrolysis include water; lower alcohols such as ethanol, methanol or the like; ethers such as dimethyl ether, diethyl ether, dimethoxyethane, dioxane, tetrahydrofuran, or the like; halogenated hydrocarbons such as dichloromethane, chloroform or the like; tertiary amines such as pyridine, triethylamine or the like; or a mixture of two or more of the solvents mentioned above. The reaction is usually carried out a temperature of from about 0 to 100°C, preferably at room temperature to 50°C, for 1 to 48 hours, preferably for 2 to 5 hours.

In yet another aspect, the present invention provides novel compounds of the formula



(IX)

wherein R_1, R_2, R_3, R_4, R_5, X and the dotted line in ring A are as defined with respect to formula (I) above. The 11-keto compounds of formula (IX) can be prepared by the procedures described hereinabove for the preparation of

62 the corresponding 11β-hydroxy compounds of formula (I). Thus, a starting material corresponding to formula (II) but having an 11-keto group is reacted with R_2OCOCl or R_2OCOBr, to afford the corresponding novel intermediate corresponding to formula (III) but having an 11-keto group; that intermediate is then converted to its metal salt, which corresponds to formula (IV) except for the 62 presence of an 11-keto instead of an 11β-hydroxy group; and the metal salt is then reacted with R_1W to afford the corresponding compound of formula (IX). All reaction conditions are as previously described with respect to the corresponding processes for preparing the corresponding compounds of formula (I). Also, the preparation of the compounds of formula (IX) wherein R_1 is a sulfinyl- or sulfonyl- containing grouping or wherein R_3 is hydroxy generally proceeds as a final step in the synthetic scheme in a manner analogous to that used for the corresponding compounds of formula (I). Further, all of the above described alternative processes for the preparation of the compounds of formula (I) are equally applicable to the preparation of the compounds of formula (IX) by simply substituting the 11-oxo starting material for the 62 corresponding 11β-hydroxy steroids used therein, e.g., replacing the 11-hydroxy group in formulas (V), (VI), (VII), (VIII), (X) and (XI) with an 11-oxo group and otherwise proceeding as described hereinabove for the 43 reactions (II)⟶(V)⟶(VI)⟶(I); (III)⟶(VIII)⟶ L (I); (VI)⟶(VII)⟶(I); (II)⟶(X)⟶(I); (VI)⟶(I), etc.

Also, the compounds of formula (IX) can be prepared by reacting the corresponding compounds of formula (I) with an oxidizing agent. The oxidation of a

compound of formula (I) in order to convert it into the corresponding compound of formula (IX) is usually carried out by using an oxidizing agent in an appropriate solvent. The solvent may be any conventional solvent, for example, water, an organic acid (e.g. formic acid, acetic acid, trifluoroacetic acid), an alcohol (e.g. methanol, ethanol), a halogenated hydrocarbon (e.g. chloroform, dichloromethane), or the like. The oxidizing agent may also be any conventional agent which is effective for oxidizing a hydroxy group to a carbonyl group, for example, pyridinium chlorochromate, chromium trioxide in pyridine, hydrogen peroxide, dichromic acid, dichromates (e.g. sodium dichromate, potassium dichromate), permanganic acid, permanganates (e.g. sodium permanganate, potassium permanganate), or the like. The oxidizing agent is usually used in an amount of 1 mole or more, preferably 1 to 3 mole, per mole of the compound of formula (I). The reaction is usually carried out at a temperature of 0 to 40°C, preferably at around room temperature, for about 6 to 30 hours.

The novel compounds of formula (IX) are useful as soft steroidal anti-inflammatory agents and also *in vivo* or *in vitro* precursors of the corresponding 11β-hydroxy compounds. Thus, the compounds of formula (IX) can be reduced *in vitro* to afford the corresponding compounds of formula (I), using a reducing agent known to be capable of reducing the 11-oxo group to an a 11β-hydroxy group without modifying the remainder of the steroidal starting material. Typically, microbiological reduction is advantageous for carrying out the desired conversion, although chemical reduction also is possible. Further, the compounds of formula (IX) may be formulated into appropriate dosage forms (e.g., retention enemas) for the

treatment of conditions such as ulcerative colitis. In such dosage forms, it is thought that the compounds of formula (IX) are microbiologically reduced by bacteria in the body (e.g. in the colon) to the highly active 11β-hydroxy steroids, which elicit the desired anti-inflammatory response.

The preferred compounds of formula (IX) are those which are precursors of the preferred compounds of formula (I) wherein Z is β-hydroxymethylene, namely corresponding 11-keto compounds of formula (IX). An especially preferred group of compounds of formula (IX) consists of those wherein X, R_1 and R_2 are defined as above with respect to formula (I) and the remaining structural variations are identical to those of cortisone (i.e. R_3, R_4 and R_5 are each a hydrogen atom and the 1,2-linkage is saturated), of prednisone (i.e. R_3, R_4 and R_5 are each hydrogen and the 1,2-linkage is unsaturated), or of the 6α- and/or 9α-fluoro and the 16α- or 16β-methyl congeners thereof, particularly when R_1 and R_2 are as defined with respect to the "first" group of preferred compounds set forth hereinabove. Most especially preferred of these derivatives are those wherein X is oxygen, R_2 is C_1-C_6 alkyl and R_1 is C_1-C_6 alkyl, C_1-C_6 (monohalo)alkyl [particularly chloromethyl] or $-CH_2-Y-(C_1-C_6$ alkyl) [particularly $-CH_2-Y-CH_3$].

The results of various activity studies of representative species of the invention, discussed in detail below, clearly indicate the potent anti-inflammatory activity and the minimal systemic activity/toxicity of the soft steroids of formula (I). In view of this desirable separation of local and systemic activities, the compounds of the invention can be used in the treatment of topical or other localized inflammatory conditions without causing the serious systemic side effects typically exhibited by the known natural and synthetic glucocorticosteroids such as cortisone, hydrocortisone, hydrocortisone 17α-butyrate,

betamethasone 17-valerate, triamcinolone, betamethasone dipropionate and the like.

THYMUS INVOLUTION TEST

The test animals were female Sprague/Dawley rats weighing approximately 40-45 grams each. One side of each ear of each rat was treated with a total of 25 microliters of a solution (ethanol/isopropyl myristate or acetone/isopropyl myristate, 90/10) containing the amount of test compound indicated below. Animals which were treated identically, save for omission of the test compound, served as controls. After 24 hours, all rats were sacrificed and weighed, and their thymi were removed and weighed. The results are tabulated in Table I below, the weights of the thymi being expressed as mg/100 g of rat.

TABLE I

Effect of topically administered soft steroids and reference steroids on thymus weight in rats.

Test Compound	Amount of Test Compound Applied (μmol)	Number of Rats	mg Thymus ±SD 100 g Rat	Total Weight per Rat (g) Starting	Final	% Gain ±SD
None (Control)	--	8	364±29	48.44	61.42	27±6
Hydrocortisone	0.75	8	274±45	49.44	61.15	24±7
Chloromethyl 11β-hydroxy-17α-methoxycarbonyl-oxyandrost-4-en-3-one-17β-carboxy-late	0.75	8	347±31	48.06	62.10	29±5
Chloromethyl 17α-ethoxycar-bonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate	0.75	7	309±24	45.57	60.60	33±6

The change in weight in the thymi is a measure of systemic activity and hence of toxicity. The lower the weight of the thymi, the greater the systemic activity. As can be seen from the above data, even hydrocortisone, the natural glucocorticoid, causes a significant decrease in thymus weight compared to the control. The decreases caused by equal doses of representative species of the invention are much less significant, indicating those compounds have much less systemic activity than hydrocortisone.

BLANCHING STUDIES

McKenzie-type human blanching studies were undertaken to study the blanching effects of a representative test compound of the invention, chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β carboxylate. The ability of a compound to cause blanching in humans has been found to correlate closely with its anti-inflammatory activity.

The test compound was dissolved in ethanol/isopropyl myristate (90/10 or 70/30) at 0.03, 0.01, 0.003, 0.001 and 0.0003 M concentrations. 50 Microliter aliquots of each solution were applied to separate gauze portions of a bandage of the type commonly used for allergy testing and the bandage was applied to the forearm. After 6 hours of occlusion, the bandage was removed. After 1 to 5 hours after removal of the bandage, blanching was observed even at the lowest concentrations of test compound.

When hydrocortisone was tested according to the above procedure comparing it directly to the test compound, blanching was not observed at concentrations of hydrocortisone below 0.03 M. Further, it was noted that

0.03 M hydrocortisone caused approximately the same degree of blanching as that resulting from use of 0.001 M chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate.

EAR EDEMA TEST

The test animals were Sprague/Dawley rats weighing approximately 150 grams each. In treatment groups, selected amounts of the test compound were dissolved in acetone containing 5% croton oil and 50 microliters of the solution were applied to the inner surface of the right ear of the rats. A control group was identically treated with vehicle only, i.e. 5% croton oil in acetone. Six hours after croton oil challenge, a constant region of each ear was removed by dissection under anesthesia. Then, 48 hours after steroid treatment, the animals were sacrificed and the thymi and adrenals were removed and weighed. The test results showing the inhibitory effect of topically applied steroids on the ear swelling induced by croton oil are summarized in Table II below.

TABLE II

Effect of topically applied soft steroid and reference steroids on ear swelling induced by croton oil.

Test Compound	Dose[a] mg/kg	Number of Test Animals	Ear Weight (mg)[b] Inflamed Ear	Untreated Ear
None (Control)		5	75.2±4.5	46.6±1.4
Chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate	0.3	5	62.2±3.0*	50.8±2.4
	1	5	55.0±2.6**	48.4±1.0
	3	5	52.6±1.8**	51.6±3.2
Hydrocortisone 17-butyrate	1	5	50.0±2.3**	52.0±2.5
Betamethasone 17-valerate	1	5	55.4±1.2*	50.4±2.0

a : calculated values based on application of 50 µl of steroid solution.

b : 50 µl of 5% croton oil/acetone and drugs in 5% croton oil/acetone were applied to the right ear. Ear weight was measured 6 hr after topical application.

*:p<0.05; **:p<0.01: Significant difference from control.

TABLE II Continued

Test Compound	%Increase	%Inhibition	Relative Organ Weight (mg/100g body wt.) Thymus	Adrenals
None (Control)	61.4±0.9		333±15	23.3±1.7
Chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate	23.3±7.2*	62.1	290±25	26.0±2.5
	14.0±6.5**	77.2	293±21	18.7±1.4
	3.7±8.1**	94.0	288±21	20.3±0.8
Hydrocortisone 17-butyrate	-3.6±3.5**	106.0	303±21	20.2±0.7
Betamethasone 17-valerate	10.9±6.3**	82.2	267±19*	18.9±1.9

*:p<0.05; **:p<0.01: Significant difference from control.

As can be seen from Table II above, the representative species of the present invention, namely chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, substantially inhibited the swelling (and consequent increased weight) of the ear caused by croton oil, i.e., the compound exhibited substantial anti-inflammatory activity. On the other hand, in contrast to the effect caused by betametasone 17-valerate, the representative compound of the invention did not significantly decrease the thymus weight as compared to the control, i.e., it did not show a significant degree of systemic activity.

GRANULOMA FORMATION TEST

The test compound was dissolved in acetone and aliquots of varying concentrations were injected into cotton pellets. The pellets were dried and then one pellet was implanted beneath the skin of each test rat. Six days later, the animals were sacrificed and the granulation tissue (granuloma) which formed in and around the implanted pellet was removed, dried and weighed. In addition, the thymi and adrenals were removed and weighed. The ability of a compound to inhibit granuloma formulation in this test is a direct indication of local anti-inflammatory activity; thus, the lower the weight of granulation tissue, the better the anti-inflammatory activity. On the other hand, a significant decrease in thymus weight is indicative of significant systemic activity; conversely, when a test compound does not significantly decrease thymus weight as compared to the control, such is indicative of a lack of (or very minimal) systemic side effects.

The results are tabulated in Tables III, IV and V-a and V-b below.

TABLE III

Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

Test Compound	Dose (mg/ pellet)	Number of Test Animals	Body wt. gain (g)
None (Control)		10	40.5±0.8
Chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate	0.1	8	36.0±2.8
	0.3	8	33.0±1.3***
	1	8	32.8±0.9***
	3	7	30.7±1.5***
Chloromethyl 11β-hydroxy-17α-methoxy-carbonyloxyandrost-4-en-3-one-17β-carboxylate	1	7	33.4±1.3***
Hydrocortisone 17-butyrate	1	8	33.4±1.4***
	3	8	15.9±1.4***
	10	8	4.9±1.0***
Betamethasone 17-valerate	1	8	16.6±1.9***
	3	8	14.9±1.7***
	10	8	17.0±2.1***

(Mean±S.E.)

***, p<0.001.

TABLE III continued

Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

Test Compound	Granulation tissue		Relative organ weight mg/100g body wt. (Decrease %)	
	Dry wt. (mg/100g body wt.)	Inhibition (%)	Thymus	Adrenals
None (Control)	43.7±4.2		326±22	23.7±1.1
Chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate	34.7±4.3	20.6	282±13 (13.5)	22.9±2.6 (3.4)
	25.3±2.3**	42.1	298±16 (8.6)	22.8±1.0 (3.8)
	14.0±1.8***	68.0	304±10 (6.7)	21.8±1.3 (8.0)
	18.7±2.3***	57.2	278±21 (14.7)	19.6±1.1* (17.3)
Chloromethyl 11β-hydroxy-17α-methoxy-carbonyloxyandrost-4-en-3-one-17β-carboxylate	24.6±2.6**	43.7	218±15** (33.1)	19.1±1.1** (19.4)
Hydrocortisone 17-butyrate	32.2±5.0	26.3	73±5 *** (77.6)	27.1±1.4 (-14.3)
	21.6±2.2**	50.6	47±3 *** (85.6)	16.5±1.2*** (30.4)
	29.2±3.1*	33.2	32±3 *** (90.2)	16.8±1.2*** (29.1)
Betamethasone 17-valerate	35.4±7.3	19.0	47±2 *** (85.6)	15.5±1.3*** (34.6)
	31.6±2.1*	27.7	38±3 *** (88.3)	13.6±0.9*** (42.6)
	40.7±2.6	6.9	43±4 *** (86.8)	12.6±0.9*** (46.8)

*, $p<0.05$, **, $p<0.01$, ***, $p<0.001$. (mean±S.E.)

TABLE IV

Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

Test Compound	Dose (µg/pellet)	Number of Test Animals	Body wt. gain (g)
None (Control)		10	32.4±1.4
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androst-4-en-3-one-17β-carboxylate	100	8	34.9±2.7
	300	8	33.9±1.6
	1000	8	34.0±2.6
	3000	8	32.4±2.3
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androsta-1,4-dien-3-one-17β-carboxylate	30	8	32.4±1.2
	100	7	35.0±1.5
	300	8	34.4±1.1
	1000	8	29.4±1.5
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	0.3	8	32.4±1.1
	1	8	37.3±1.5*
	3	8	34.3±1.1
	10	8	36.1±1.1
	30	8	31.3±1.4
Chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate	1	7	33.0±1.7
	3	8	30.4±1.1
	10	8	33.0±1.5
	30	8	31.8±1.7
Hydrocortisone 17-butyrate	300	6	26.2±1.7*
	1000	6	26.2±1.2**
	3000	6	6.7±2.2***
	10000	6	-2.0±2.4***
Betamethasone 17-valerate	100	7	24.9±1.9**
	300	8	22.3±1.2***
	1000	7	5.3±1.0***
	3000	8	6.6±1.4***

*, $p<0.05$, **, $p<0.01$, ***, $p<0.001$. (Mean±S.E.)

TABLE IV continued

Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

Test Compound	Granulation tissue				Thymus wt.	
	Wet wt. (mg)	Inhibition (%)	Dry wt. (mg)	Inhibition (%)	mg	(Decrease %)
None (Control)	566±28		81.2±6.3		445±20	
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androst-4-en-3-one-17β-carboxylate	485±36	14.3	70.0±6.0	13.8	452±29	
	431±20**	23.9	50.9±2.8**	37.3	469±25	
	305±16***	46.1	24.1±2.7***	70.3	464±30	
	292±7 ***	48.4	20.3±1.3***	75.0	459±24	
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androsta-1,4-dien-3-one-17β-carboxylate	432±15**	23.7	51.0±2.8**	37.2	523±26*	
	417±27**	26.3	41.1±5.8***	49.4	537±31*	
	369±18***	34.8	38.1±5.9***	53.1	525±28*	
	289±12***	48.9	18.5±2.4***	77.2	423±26	
Chloromethyl 17α-ethoxy-carbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	472±23*	16.6	57.3±5.0*	29.4	492±26	
	388±31***	31.4	36.4±2.4***	55.2	519±22*	
	331±11***	41.5	27.4±2.9***	66.3	472±16	
	313±13***	44.7	22.1±3.6***	72.8	521±35	
	290±10	48.8	20.4±2.4***	74.9	505±26	
Chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxy-carbonyloxy-16β-methyl-androsta-1,4-dien-3-one-17β-carboxylate	423±19**	25.3	44.4±5.4***	45.3	526±30*	
	351±19***	38.0	26.9±4.4***	66.9	471±20	
	362±8 ***	36.0	29.9±3.3***	63.2	474±25	
	315±12***	44.3	19.9±2.3***	75.5	489±26	
Hydrocortisone 17-butyrate	333±21***	41.2	34.0±5.3***	58.1	353±37*	(20.7)
	366±24***	35.3	35.3±4.2***	56.5	99±7 ***	(77.8)
	329±14***	41.9	28.0±2.7***	65.5	58±5 ***	(87.0)
	311±7 ***	45.1	27.2±2.4***	66.5	46±7 ***	(89.7)
Betamethasone 17-valerate	400±19***	29.3	41.1±2.7***	49.4	364±24*	(18.2)
	347±15***	38.7	33.3±3.6***	59.0	264±29***	(40.7)
	363±28***	35.9	38.1±4.8***	53.1	77±5 ***	(82.7)
	374±15***	33.9	43.0±4.1***	47.0	63±3 ***	(85.8)

*, p<0.05, **, p<0.01, ***, p<0.001. (Mean±S.E.)

TABLE V -a

Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

Test Compound	Dose (µg/pellet)	Number of Test Animals	Body wt. gain (g)
None (Control)		10	33.5±1.0
Chloromethyl 17α-ethoxy-carbonyloxy-9α-fluoro-11β-hydroxy-16β-methyl-androsta-1,4-dien-3-one-17β-carboxylate	0.3	8	32.5±1.1
	1	8	36.3±0.9
	3	8	33.8±1.3
	10	8	31.1±1.7
Chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	0.3	8	35.6±1.0
	1	8	31.9±0.8
	3	7	34.1±1.9
	10	8	33.1±1.6
Betamethasone 17-valerate	10	6	31.8±1.6
	30	6	30.8±3.0
	100	6	25.7±1.2***
Clobetasol 17-propionate	1	8	33.0±1.2
	3	7	24.9±1.0***
	10	8	25.0±2.1**
	30	8	24.8±1.1***
	100	8	15.9±1.0***

*, p< 0.05, **,p< 0.01, ***, p <0.001. (Mean±S.E.)

TABLE V-a (continued)

Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

Test Compound	Granulation Tissue				Thymus wt.	
	Wet wt. (mg)	Inhibition (%)	Dry wt. (mg)	Inhibition (%)	mg	(Decrease %)
None (Control)	525±19		80.1±5.1		495±36	
Chloromethyl 17α-ethoxy-carbonyloxy-9α-fluoro-11β-hydroxy-16β-methyl-androsta-1,4-dien-3-one-17β-carboxylate	499±36	5.0	61.8±5.7*	22.8	501±29	
	437±24*	16.8	57.0±6.2*	28.8	566±31	
	422±32*	19.6	47.5±5.0***	40.7	500±27	
	370±21***	29.5	34.8±5.5***	56.6	421±30	
Chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	454±27*	13.5	55.1±6.2**	31.2	523±28	
	415±30**	21.0	42.9±5.1***	46.4	453±21	
	360±18***	31.4	29.7±3.2***	62.9	504±42	
	350±13***	33.3	28.5±2.8***	64.4	547±26	
Betamethasone 17-valerate	375±19***	28.6	38.5±6.2***	51.9	479±25	(3.2)
	412±42*	21.5	46.2±7.4**	42.3	484±23	(2.2)
	419±20**	20.2	41.0±4.2***	48.8	378±30*	(23.6)
Clobetasol 17-propionate	401±29**	23.6	42.0±5.8***	47.6	478±22	(3.4)
	402±40**	23.4	43.1±8.9**	46.2	449±21	(9.3)
	364±25***	30.7	37.9±6.8***	52.7	322±22**	(34.9)
	320±10***	39.0	25.5±2.1***	68.2	174±26***	(64.8)
	325±12***	38.1	23.9±3.3***	70.2	84±3 ***	(83.0)

*, p <0.05, **, p <0.01, ***, p <0.001. (Mean±S.E.)

Table V-b

Effect of locally administered soft steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

Test Compound	Dose (ug/pellet)	Number of Test animals	Body wt. gain (g)	Dry granulation Tissue mg	Dry granulation Tissue Inhibition %	Thymus wt. mg
None (Control)	——	10	28.0±1.5	67.2±3.4		505±22
Chloromethyl 9α-fluoro-17α-	1	8	28.9±1.1	59.1±5.8	12.1	441±24
isopropoxycarbonyloxy-16β-	3	8	25.8±0.9	49.4±3.7**	26.5	519±31
methylandrosta-1,4-dien-	10	7	28.4±0.8	51.1±5.8*	24.0	547±35
3,11-dione-17β-carboxylate	30	8	27.4±0.9	40.6±3.6***	39.6	536±24
Chloromethyl 17α-ethoxy-	1	7	23.7±1.5	55.3±2.6*	17.7	459±41
carbonyloxy-9α-fluoro-16α-	3	8	25.6±1.2	51.6±5.9*	23.2	467±21
methylandrosta-1,4-dien-	10	8	26.5±2.5	41.5±4.7***	38.2	544±31
3,11-dione-17β-carboxylate	30	8	20.3±0.9**	39.9±3.6***	40.6	463±24

*, p 0.05, **, p 0.01, ***, p 0.001. (Mean+S.E.)

Male Sprague-Dawley rats, weighing 152-189g (mean body weight 171g), were used.

Cotton pellet weight was 30.1+0.3 mg (number of test animals were 30).

The test data in Tables III, IV and V-a and V-b above clearly show that the representative compounds of the present invention exhibited a significant anti-inflammatory response at lower dosages than did the prior art steroids, hydrocortisone 17-butyrate and betamethasone 17-valerate. On the other hand, all of the prior art steroids dramatically decreased the weight of the thymi and thus showed very potent systemic activity, while the representative compounds of the invention either did not significantly decrease the thymi weights or only minimally decreased the thymi weight. Thus, the present compounds have a much greater therapeutic index, i.e., separation of local anti-inflammatory from systemic activity, than do the prior art steroidal anti-inflammatory agents.

Also the test data in Table V-b above shows that the representative compounds of the present invention exhibited a significant local anti-inflammatory activity.

From the results tabulated in Tables IV and V-b, the ED_{40}'s, ED_{50}'s and ED_{60}'s and the relative potencies of representative compounds of the invention were calculated and are shown in Table VI below. One of the compounds of the invention, namely chloromethyl 11 β-hydroxy-17 -isopropoxycarbonyloxyandrost-4-en-3-one-17 β-carboxylate, has been assigned a potency value of 1 at each ED level, and the potencies of the other compounds are expressed relative thereto. The ED_{40}'s, ED_{50}'s and ED_{60}'s are the dosages required to achieve, respectively, 40%, 50% and 60% reduction in the weight of the granulation tissue.

TABLE VI

Relative potencies of soft steroids in the local cotton pellet granuloma assay.

Test Compound	ED_{40}[1] (µg/pellet)	Relative potency	ED_{50}[2] (µg/pellet)	Relative potency	ED_{60}[3] (µg/pellet)	Relative potency
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate	307 (238-394)	1	460 (360-623)	1	690 (523-1023)	1
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	47 (15-85)	6.5	119 (60-202)	3.9	301 (170-627)	2.3
Chloromethyl 17α-ethoxy-carbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	0.47 (0.23-0.75)	653	1.07 (0.66-1.59)	430	2.44 (1.65-3.86)	283
Chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate	0.25 (0.004-0.886)	1228	0.97 (0.08-2.31)	474	3.75 (1.25-7.68)	184
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate	2.31 (1.07-6.38)	133	6.45 (2.96-44.58)	71	18.01 (6.47-393.8)	38
Chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	0.58 (0.20-1.01)	529	1.20 (0.67-2.88)	383	2.49 (1.37-13.32)	277
Hydrocortisone 17-butyrate	———	———	———	———	1015 (724-26866)	0.7
Clobetasol 17-propionate	———	———	>3	———	>10	———

1 dose causing 40% inhibition of granulation tissue weight.

2 dose causing 50% inhibition of granulation tissue weight.

3 dose causing 60% inhibition of granulation tissue weight.

( ) = 95% confidence limits

THYMUS INHIBITION TESTING

Several further studies were undertaken to determine the effects of selected compounds of the invention on thymi weights in rats when the drugs were systemically administered. In each of these studies, male Sprague-Dawley rats were used. (For average weight of rats for each study, see the tables which follow.) The test compounds were suspended in 0.5% CMC (carboxymethylcellulose) and injected subcutaneously once daily for three days. On the fifth day (48 hours following the last treatment), the animals were sacrificed and the thymi weights were recorded. Body weight gains were measured 24 hours after the last treatment. The test results are set forth in Tables VII, VIII and IX below. The TED_{40}'s, TED_{50}'s (thymolytic effective doses or doses required to achieve 40% and 50% inhibition of thymi weight, respectively) and relative potency of representative compounds of the invention and reference steroids are shown in Table X below. In Table X, the TED_{40} and TED_{50} for the reference steroid betamethasone 17-valerate has each been assigned a value of 1, and the potencies of the other compounds are expressed relative thereto. It is evident that the higher the inhibition of thymus activity at a given dose, the more toxic the compound is.

TABLE VII

Effects of systemically administered (s.c.) soft steroids and reference steroids on body weight and thymus weight in rats.

Test Compound	Dose (mg/kg/day)	Number of Test Animals	Body weight gain (g)	Thymus (mg)	Inhibition (%)
None (Control)		9	18.3±0.7	471±21	
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androst-4-en-3-one-17β-carboxylate	3	9	14.7±0.6**	439±18	6.8
	10	10	10.2±0.7***	386±17**	18.0
	30	10	6.8±2.1***	291±22***	38.2
	100	10	2.8±1.8***	185±17***	60.7
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyl-oxyandrosta-1,4-dien-3-one-17β-carboxylate	3	9	9.0±0.9***	377±16**	20.0
	10	9	6.2±0.7***	312±23***	33.8
	30	10	4.8±1.4***	257±24***	45.4
	100	10	0.3±1.6***	161±19***	65.8
Chloromethyl 17α-ethoxy-carbonyloxy-9α-fluoro-11β-hydroxy-16α-methyl-androsta-1,4-dien-3-one-17β-carboxylate	1	10	13.1±1.0***	428±20	9.1
	3	9	12.7±1.4**	412±20	12.5
	10	10	9.7±1.3***	405±21*	14.0
	30	10	4.4±0.7***	292±15***	38.0
Hydrocortisone 17-butyrate	0.3	10	17.0±0.8	441±27	6.4
	1	10	11.8±0.8***	323±16***	31.4
	3	10	7.3±0.5***	166±5 ***	64.8
	10	10	-5.0±1.1***	65±5 ***	86.2
Betamethasone 17-valerate	0.1	10	15.5±0.9*	362±16***	23.1
	0.3	10	12.4±0.9***	276±11***	41.4
	1	10	13.0±1.1***	200±14***	57.5
	3	10	9.9±1.3***	119±7 ***	74.7

*, $p<0.05$, **, $p<0.01$, ***, $p<0.001$ (Mean±S.E.)

Male Sprague-Dawley rats, weighing 149-168g, were used.

TABLE VIII

Effects of systemically administered (s.c.) soft steroids and reference steroids on body weight and thymus weight in rats.

Test Compound	Dose (mg/kg/day)	Number of Test Animals	Body weight gain (g)	Thymus wt. (mg)	Inhibition (%)
None (Control)		10	18.9±0.6	550±24	
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methyl-androsta-1,4-dien-3-one-17β-carboxylate	10	7	14.2±1.9	533±31	3.1
Chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	10	7	2.7±1.9***	234±31***	57.5
Chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate	10	7	5.3±1.4***	260±26***	52.7
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate	10	7	2.4±1.8***	266±20***	51.6
Chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxy-androsta-1,4-dien-3-one-17β-carboxylate	10	7	2.7±1.7***	277±25***	49.6
Clobetasol 17-propionate	0.003	8	18.2±0.6	537±28	2.4
	0.01	8	15.5±1.1*	498±15	9.5
	0.03	8	12.3±1.3**	363±22***	34.0
	0.1	8	-0.4±1.3***	149±9 ***	72.9
	0.3	8	-14.3±1.3***	63±3 ***	88.5

*, $p<0.05$, ** $p<0.01$, ***, $p<0.001$.

(mean±S.E.)

Male Sprague-Dawley rats, weighing about 185g (162-209g), were used.

TABLE IX

Effects of systemically administered (s.c.) soft steroids on body weight and thymus weight in rats.

Test Compound	Dose (mg/kg/day)	Number of Test Animals	Body weight gain (g)	Thymus wt. (mg)	Decrease (%)
None (Control)		10	21.2±0.9	426±17	
Chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	3	7	18.8±1.4	426±19	0.0
	10	7	13.8±1.6***	354±8 **	16.9
	30	7	12.0±0.8***	282±11***	33.8
	100	7	9.8±1.3***	206±15***	51.6
Chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-pentyloxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	1	7	18.0±1.5	387±23	9.2
	3	7	15.6±1.3**	347±15**	18.5
	10	7	17.4±1.5*	357±22*	16.2
	30	7	13.5±1.0***	335±17**	21.4

*, $p<0.05$, **, $p<0.01$, ***, $p<0.001$ (Mean±S.E.)

Male Sprague-Dawley rats, weighing 91-112g, were used.

TABLE X

Thymolytic activities of soft steroids administered subcutaneously to rats.

Compound	TED_{40} (mg)	Relative Potency	TED_{50} (mg)	Relative Potency
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate	31.0 (23.9-41.9)	0.01	58.5 (43.1-87.1)	0.01
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	16.2 (11.2-23.2)	0.02	35.3 (24.6-57.5)	0.02
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	51.5 (26.5-290.0)	0.0058	> 51.5[a]	<0.011
Hydrocortisone 17-butyrate	1.3 (1.1-1.5)	0.23	2.0 (1.7-2.3)	0.29
Betamethasone 17-valerate	0.30 (0.24-0.36)	1	0.58 (0.49-0.69)	1
Clobetasol 17-propionate	0.035 (0.030-0.039)	8.6	0.052 (0.046-0.059)	11.2

[a] Even at a dosage level of 100 mg/kg/day, 50% reduction in thymus weight could not be achieved.

BLANK COTTON PELLET GRANULOMA ASSAY

A further test was undertaken to determine the thymolytic activity of a representative species of the invention as compared to betamethasone 17-valerate. In this test, the drugs were administered intravenously to rats, while using a blank cotton pellet granuloma assay. Male Sprague-Dawley rats, each weighing about 185 grams (166-196 grams), were used. Two cotton pellets, each weighing 30 mg and containing no test compounds, were sterilized and implanted subcutaneously into the back of each test animal. This day was considered day 0 of implantation. Test compounds suspended in 0.8% polysorbate 80 were administered intravenously once daily for 3 consecutive days beginning with day 1. On day 5, the animals were sacrificed and the two pellets, with their respective granulomas, were removed, dried overnight in an oven at 50°C and weighed (dry granuloma weight). The thymi and final body weights were also recorded. The results are given in Table XI below.

In the foregoing tests, there was determined the deactivation of the representative species of the present soft steroids administered intravenously to rats. The ratio between the potencies of the test steroids and betamethasone 17-valerate against local anti-inflammation was 283:0.7 as seen from Table VI. This means that the test compounds exhibit a local anti-inflammatory activity which is approximately 400 times as high as the activity of the betamethasone 17-valerate. The test compounds were administered intravenously to rats to check the test compounds also for systemic anti-inflammatory activity as compared to betamethasone 17-valerate. The test compounds were found lower in the inhibition of granulation tissue formation and also in the thymus involution activity than betamethasone 17-valerate. From the results of the tests, it is presumed that the compounds which will not be readily subjected to metabolism (deactivation) have a systemic anti-inflammatory activity, as is the case with betamethasone 17-valerate.

TABLE XI

Thymolytic activities of test steroids administered intravenously to rats in the blank cotton pellet granuloma assay.

Test Compound	Dose (mg/kg/day)	Number of Test Animals	Body wt. gain (g)	Dry granuloma wt. (mg)	Inhibition (%)	Thymus wt. (mg)	Decrease (%)
None (Control)		7	21.4±1.3	62.7±6.1		422±27	
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	1	7	14.1±1.4**	50.1±6.9	20.1	373±25	11.6
	3	6	14.2±1.3**	49.3±5.1	21.4	338±20*	19.9
	10	6	0.3±1.7***	45.7±4.6	27.1	209±31***	50.5
	30	6	-18.5±2.3***	32.7±3.0**	47.8	71±4 ***	83.2
Betamethasone 17-valerate	0.1	7	14.4±1.6**	49.3±3.9	21.4	305±14**	27.7
	0.3	5	12.2±1.1***	44.4±2.8*	29.2	288±27**	31.8
	1	7	12.9±1.1***	46.1±4.3*	26.5	233±15***	44.8
	3	7	13.0±2.5*	47.3±2.7	24.6	167±22***	60.4

(Mean±S.E.)

*, $p<0.05$, **, $p<0.01$, ***, $p<0.001$.

The ED_{50}'s calculated for the local cotton pellet granuloma assay (as shown, for example, in Table VI above) and the TED_{40}'s calculated on the basis of thymus inhibition testing (as shown, for example, in Table X above) were used to arrive at relative potency and a therapeutic index for representative species of the invention as compared to prior art steroids. See Table XII below, which clearly shows the potent anti-inflammatory activity and minimal systemic toxicity of the compounds of the present invention.

TABLE XII

Therapeutic Indices of representative species of the invention as compared to prior art steroids.

Compound	ED_{50} [a]	Relative Potency	TED_{40} [b]	Relative Potency	Therapeutic Index [c]
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate	460 (360-623)	1	31.0 (23.9-41.9)	1/24	24
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	119 (60-202)	4	16.2 (11.2-23.2)	1/12	48
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	1.07 (0.66-1.59)	450	51.5 (26.5-290.0)	1/40	18000
Chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	2.38 (1.60-3.78)	202	46.0 (36.0-62.1)	1/36	7270
Hydrocortisone 17-butyrate	480 (313-892)	1	1.3 (1.1-1.5)	1	1
Betamethasone 17-valerate	100	5	0.3 (0.24-0.36)	4	1

[a] for the anti-inflammatory effect in cotton pellet granuloma (μg/pellet)

[b] for the thymus inhibition effect required subcutaneously (mg/kg)

[c] the ratio of the relative potency for the ED_{50} to the relative potency for the TED_{40} hydrocortisone 17-butyrate has been assigned a value of one

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The compounds of formula (I) can be combined with suitable non-toxic pharmaceutically acceptable carriers to provide pharmaceutical compositions for use in the treatment of topical or other localized inflammation. Obviously, in view of their lack of systemic activity, the compounds of the present invention are not intended for treatment of conditions where systemic adrenocortical therapy is indicated, e.g., adrenocortical insufficiency. As examples of inflammatory conditions which can be treated with pharmaceutical compositions containing at least one compound of the invention and one or more pharmaceutical carriers, the following can be mentioned: dermatological disorders such as atopic dermatitis, acne, psoriasis or contact dermatitis; allergic states such as bronchial asthma; ophthalmic and otic diseases involving acute and chronic allergic and inflammatory reactions; respiratory diseases; ulcerative colitis; and anorectal inflammation, pruritus and pain associated with hemorrhoids, proctitis, cryptitis, fissures, postoperative pain and pruritus ani. Such compositions may also be applied locally as a prophylactic measure against the inflammation and tissue rejection which arise in connection with transplants.

Obviously, the choice of carrier(s) and dosage forms will vary with the particular condition for which the composition is to be administered.

Examples of various types of preparations for topical/local administration include ointments, lotions, creams, powders, drops, (e.g. eye or ear drops), sprays, (e.g. for the nose or throat), suppositories, retention enemas, chewable or suckable tablets or pellets (e.g. for the treatment of aphthous ulcers) and aerosols. Ointments and creams may, for example, be formulated with an aqueous

or oily base with the addition of suitable thickening and/or gelling agents and/or glycols. Such base may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a glycolic solvent such as propylene glycol or 1,3-butanediol. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, woolfat, hydrogenated lanolin and beeswax and/or glyceryl monostearate and/or non-ionic emulsifying agents.

The solubility of the steroid in the ointment or cream may be enhanced by incorporation of an aromatic alcohol such as benzyl alcohol, phenylethyl alcohol or phenoxyethyl alcohol.

Lotions may be formulated with an aqueous or oily base and will in general also include one or more of the following, namely, emulsifying agents, dispersing agents, suspending agents, thickening agents, solvents, coloring agents and perfumes. Powders may be formed with the aid of any suitable powder base e.g. talc, lactose or starch. Drops may be formulated with an aqueous base also comprising one or more dispersing agents, suspending agents or solubilizing agents, etc. Spray compositions may, for example, be formulated as aerosols with the use of a suitable propellane, e.g., dichlorodifluoromethane or trichlorofluoromethane.

The proportion of active ingredient in the compositions according to the invention will vary with the precise compound used, the type of formulation prepared and the particular condition for which the composition is to be administered. The formulation will generally contain from about 0.0001 to about 5.0% by weight of the compound of formula (I). Topical

preparations will generally contain 0.0001 to 2.5%, preferably 0.01 to 0.5%, and will be administered once daily, or as needed. Also, generally speaking, the compounds of the invention can be incorporated into topical and other local compositions formulated substantially as are such presently available types of compositions containing known glucocorticosteroids, at approximately the same (or in the case of the most potent compounds of the invention, at proportionately lower) dosage levels as compared to known highly active agents such as methyl prednisolone acetate and beclomethasone dipropionate or at considerably lower dosage levels as compared to less active known agents such as hydrocortisone.

Thus, for example, an inhalation formulation suitable for use in the treatment of asthma can be prepared as a metered-dose aerosol unit containing a representative species of the invention such as chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, according to procedures well known to those skilled in the art of pharmaceutical formulations. Such an aerosol unit may contain a microcrystalline suspension of the aforementioned compound in suitable propellants (e.g., trichlorofluoromethane and dichlorodifluoromethane), with oleic acid or other suitable dispersing agent. Each unit typically contains 10 milligrams of the aforesaid active ingredient, approximately 50 micrograms of which are released at each actuation. When one of the more potent species of the invention, e.g. chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate, is employed, each unit typically contains 1 milligram of the active ingredient and releases approximately 5 micrograms at each actuation.

Another example of a pharmaceutical composition according to the invention is a foam suitable for treatment of a wide variety of inflammatory anorectal disorders, to be applied anally or perianally, comprising 0.1% of a compound of formula (I) such as chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, and 1% of a local anaesthetic such as pramoxine hydrochloride, in a mucoadhesive foam base of propylene glycol, ethoxylated stearyl alcohol, polyoxyethylene-10-stearyl ether, cetyl alcohol, methyl paraben, propyl paraben, triethanolamine, and water, with inert propellents. When a more potent compound of the invention is employed, less active ingredient generally is used, e.g. 0.05% of chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

Yet another pharmaceutical formulation according to the invention is a solution or suspension suitable for use as a retention enema, a single dose of which typically contains 40 milligrams of a compound of the invention such as chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate (or 20 milligrams of a more potent compound of the invention such as chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate or chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate) together with sodium chloride, polysorbate 80 and from 1 to 6 ounces of water (the water being added shortly before use). The suspension can be administered as a retention enema or by continuous drip several times weekly in the treatment of ulcerative colitis.

Other pharmaceutical formulations according to

the invention are illustrated in the examples which follow.

Without further elaboration, it is believed that one of ordinary skill in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the following examples are to be construed as merely illustrative and not limitative of the remainder of the specification and claims in any way whatsoever.

DE Cl
δ

EXAMPLE 1

To a solution of hydrocortisone (15 grams, 0.04 mol) in 120 milliliters of tetrahydrofuran and 30 milliliters of methanol at room temperature is added a warm (approximately 50°C) solution of sodium metaperiodate (25.7 grams, 0.12 mol) in 100 milliliters of water). The reaction mixture is stirred at room temperature for 2 hours, then is concentrated under reduced pressure to remove the tetrahydrofuran and methanol. The solid is triturated with 50 milliliters of water, separated by filtration, washed with water and dried in vacuo at 50°C for 3 hours. The product, 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid (i.e., cortienic acid), melts at 231-234°C, is obtained in approximately 96% yield (13.76 grams), and can be represented by the structural formula

62.60
L

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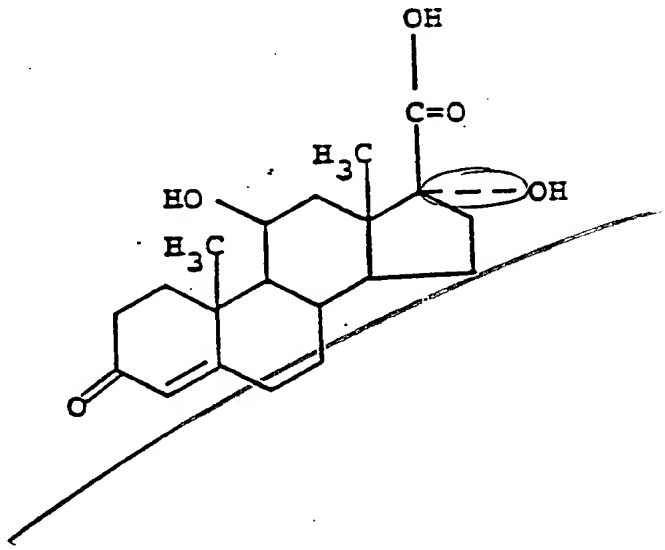

Cl
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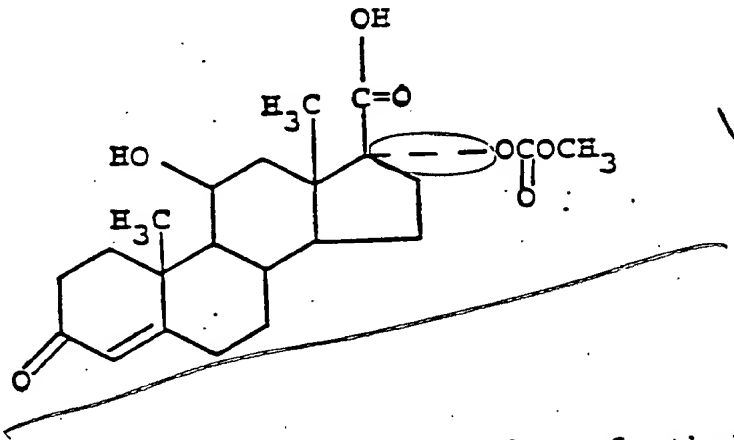
EXAMPLE 2

To a cold solution of 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid (5% weight/volume; 1 mol) and triethylamine (4 mol) in

dicholormethane is added a 50% (weight/volume) solution of methyl chloroformate (3.9 mol) in dichloromethane. The reaction mixture is allowed to warm to room temperature over a 2 hour period. The triethylamine hydrochloride precipitate which forms is removed by filtration and the filtrate is washed successively with 3% sodium bicarbonate, dilute (~1%) hydrochloric acid and water. The organic layer is separated, dried with magnesium sulfate, and filtered. The filtrate is concentrated in vacuo to a foam. The foam is used in the next step (e.g., Example 3 below) or chromatographed and crystallized for analysis. The product, 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid, melts at 198-204°C after chromatography and crystallization; ir (KBr) 3000-2800 (C-H), 1750, 1735, 1720 (C=O), 1650, 1640 (C=C-C=O) cm^{-1}. The product can be represented by the structural formula



Substitution of an equivalent quantity of ethyl chloroformate for the methyl chloroformate employed above and substantial repetition of the foregoing procedure affords 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid, melting at 192-195°C after chromatography and crystallization; ir (KBr) 3500 (11β-O-H), 3000-2800 (C-H), 1740 (C=O), 1630

(C=C-C=O) cm^{-1}; nmr($CDCl_3$) δ6.4(1, b, COOH), 5.67(1,s, C-CH), 4.43 (1,b, CHOH), 4.13 (2, q, J=7.5Hz, OCH_2CH_3); Anal. calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.76; H, 7.74.

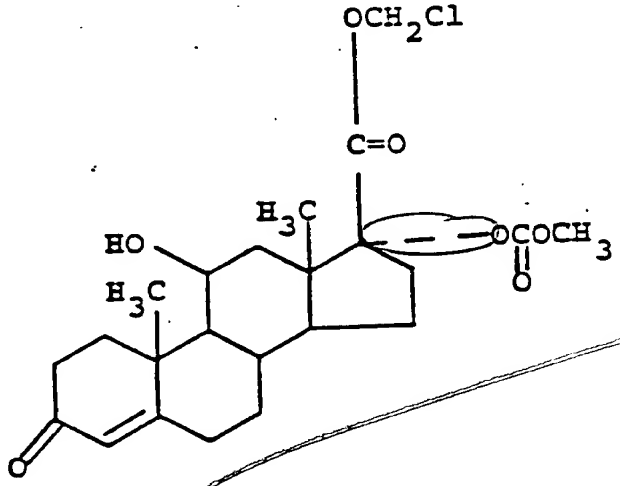
In a similar manner, substitution of an equivalent quantity of butyl chloroformate for the methyl chloroformate employed in the first paragraph of this example and substantial repetition of the procedure there detailed affords 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid. The final product, after crystallization from tetrahydrofuran-hexane, melts at 164-166°C.

Similarly, substituting an equivalent amount of isopropyl chloroformate for the methyl chloroformate used in the first paragraph of this example and repeating the procedure there detailed affords 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid. The final product, after crystallization from tetrahydrofuran-hexane, melts at 144.5-146.5°C.

EXAMPLE 3

11β-Hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid is combined with an equivalent amount of 1N sodium hydroxide in methanol and that solution is diluted to 100 times the original volume with ethyl ether. The suspension which results is refrigerated for 1 hour. Then, the crystals which form are removed by filtration, dried in an evacuated desiccator, and dissolved in hexamethylphosphoramide (10% weight/volume). A portion of the resultant solution containing 1 mole of the acid salt, i.e. of sodium 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, is combined with 4 moles of chloromethyl iodide. The

reaction mixture is maintained at room temperature for 3 hours, then is diluted to 10 times the original volume with ethyl acetate. The diluted reaction mixture is washed successively with 5% sodium thiosulfate, 3% sodium bicarbonate, and water. The organic layer is separated, dried with magnesium sulfate and filtered. The filtrate is concentrated in vacuo to a foam. The foam is purified by crystallization from a suitable solvent (ethyl ether or tetrahydrofuran/hexane). There is thus obtained chloromethyl 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, melting at 171-173°C after crystallization; ir(KBr) 3000-2800(C-H), 1760, 1748(C=O), 1650(C=C-C=O) cm^{-1}; nmr ($CDCl_3$) δ 5.67(s, 1, C=CH), 5.82, 5.62 (ABq, J=5.5Hz, 2, OCH_2Cl), 4.47(b, 1, CHOH); Anal. calcd. for $C_{23}H_{31}ClO$: C, 60.72; H, 6.87; Cl, 7.79. Found: C, 60.50; H, 7.06; Cl, 7.50. The product is characterized by the structural formula



Substitution of an equivalent quantity of 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid for the steroidal acid employed above and substantial repetition of the foregoing procedure affords, as the intermediate salt, sodium 17α-ethoxycarbonyloxy-

11β-hydroxyandrost-4-en-3-one-17β-carboxylate, and, as the final product, chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 197-200°C after crystallization; ir (KBr) 3600-3200 (O-H), 3000-2800 (C-H), 1763, 1740 (C=O), 1650 (C=C-C=O) cm^{-1}; nmr ($CDCl_3$) δ 5.7 (s, 1, C=CH), 5.81, 5.62 (ABq, J=5Hz, 2, OCH_2Cl); Anal calcd. for $C_{24}H_{33}ClO_7$: C, 61.46; H, 7.09. Found: C, 61.58; H, 7.08.

In a similar manner, substitution of an equivalent quantity of 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid for the steroidal acid employed in the first paragraph of this example and substantial repetition of the procedure there detailed affords, as the intermediate salt, sodium 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, and, as the final product, chloromethyl 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 98-100°C after crystallization; ir (KBr) 3600-3300 (O-H), 3000-2800 (C-H), 1765 (O_2C=O), 1735 (OC=O), 1650 (C=C-C=O) cm^{-1}; nmr ($CDCl_3$) δ 5.80, δ 5.60 (2, ABq, J=4.5Hz, OCH_2Cl), 5.67 (1, s, C=CH), 4.45 (1, b, CHOH), 4.08 (2, t, J=6Hz, O_2COCH_2-CH_2); Anal calcd. for $C_{26}H_{37}ClO_7$: C, 62.77; H, 7.44; Cl, 7.14. Found: C, 62.88; H, 7.23; Cl, 7.30.

Similarly, substituting an equivalent amount of 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid for the steroidal acid employed in the first paragraph of this example and substantial repetition of the procedure there detailed affords, as the intermediate salt, sodium 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, and, as the final product, chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, melting at 183.5-184.5°C after recrystallization from tetrahydrofuran-hexane.

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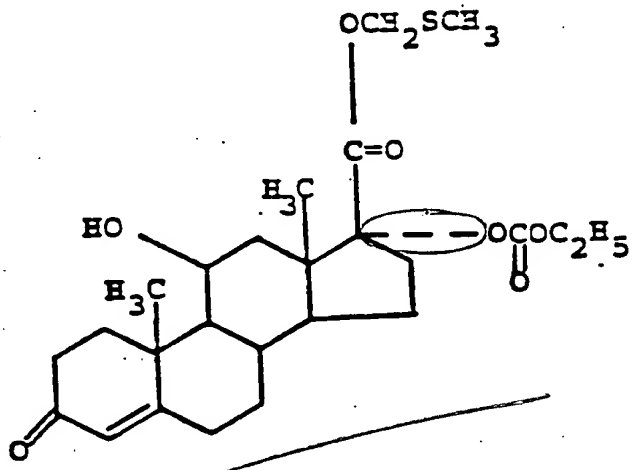
In a similar manner, an equivalent quantity of 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid is substituted for the steroidal acid and an equivalent quantity of butyl chloride is substituted for the chloromethyl iodide employed in the first paragraph of this example; and the procedure there detailed is substantially repeated, except that the step of washing with 5% sodium thiosulfate is eliminated. Obtained in this manner are the intermediate salt, sodium 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, and the final product, butyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate. The final product after crystallization from acetone melts at 148-149°C; after chromatography and crystallization, ir (KBr) 3600-3200 (O-H), 3000-2800 (C-H), 1750 (2 C=O), 1670 (C=C-C=O) cm^{-1}; nmr ($CDCl_3$) δ5.64 (s, 1, -C=CH), 4.46 (b, 1, CHOH), 4.32-4.95 (m, 4, $COOCH_2CH_3$ + $COOCH_2CH_2$-); Anal. calcd. for $C_{27}H_{40}O_7$: C, 67.99; H, 8.39. Found: C, 67.76; H, 7.74.

EXAMPLE 4

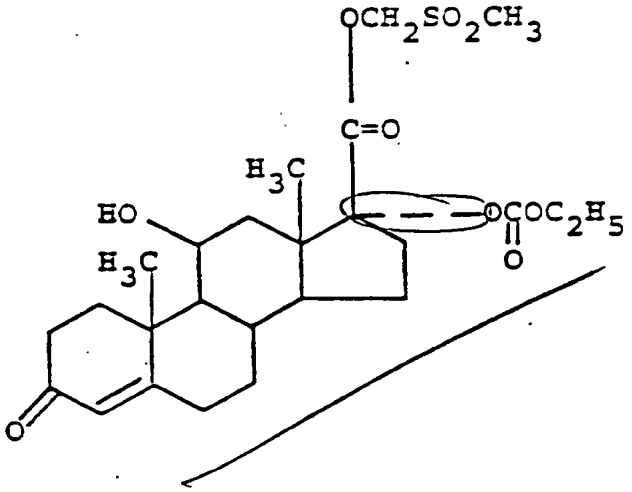
17α-Ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid (3 grams, 7.13 mmol) is treated with 7.13 milliliters of 1M methanolic sodium hydroxide solution, and 500 milliliters of ethyl ether are then added to effect precipitation. The precipitate is separated by filtration and dried in an evacuated dessicator overnight to afford 2.71 grams (6.12 mmol) of the desired salt, i.e. sodium 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, as a yellow powder. The salt is dissolved in 40 milliliters of hexamethylphosphoramide and chloromethyl methyl sulfide (2.36 grams, 24.5 mmol) is added slowly. A precipitate

of sodium chloride forms in the reaction mixture within 1 minute. The reaction mixture is stirred at room temperature for 1 hour, then is diluted with ethyl acetate to a total volume of 200 milliliters and washed successively with 3% sodium bicarbonate and water. The organic layer is separated, dried with magnesium sulfate and filtered. The filtrate is concentrated in vacuo to an oil, and the oil is chromatographed from silica gel, using ethyl acetate, chloroform and acetic acid as eluants. The chromatographed product is crystallized from a mixture of ethyl ether and hexane to give white powdery crystals of methylthiomethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 133-136°C. That product is characterized by the structural formula



To a solution of methylthiomethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate (0.48 gram, 1 mmol) in 2 milliliters of dichloromethane is added m-chloroperoxybenzoic acid (0.4 gram = 0.34 gram of peracid, 2 mmol). An exothermic reaction ensues, which subsides quickly. The reaction mixture is stirred at room temperature for 1 hour. The

precipitate which forms is removed by filtration and the filtrate is concentrated in vacuo to afford, as a white foam, methylsulfonylmethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate. That product has the structural formula



NMR ($CDCl_3$): δ5.07 (s, 2, OCH_2SO_2), 2.97 (s, 3, SO_2CH_3).

Repetition of the procedure described in the preceding paragraph, but using only 1 mmol of m-chloroperoxybenzoic acid, affords methylsulfinylmethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate.

EXAMPLE 5A

Substitution of an equivalent quantity of one of the starting materials listed below for the hydrocortisone used in Example 1 and substantial repetition of the procedure there detailed affords the indicated products:

STARTING MATERIAL	PRODUCT
fludrocortisone	9α-fluoro-11β,17α-dihydroxy-androst-4-en-3-one-17β-carboxylic acid, m.p. 250-253°C
betamethasone	9α-fluoro-11β,17α-dihydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylic acid, m.p. 248-249°C
dexamethasone	9α-fluoro-11β,17α-dihydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid, m.p. 275-278.5°C

EXAMPLE 5B

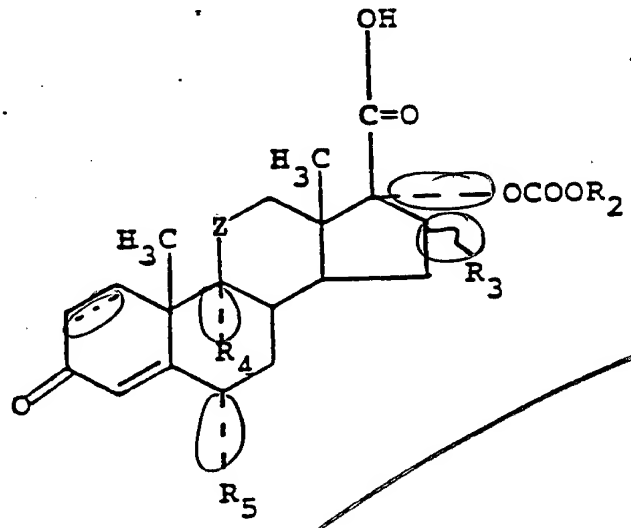
Substitution of an equivalent quantity of one of the starting materials listed below for the hydrocortisone used in Example 1 and substantial repetition of the procedure there detailed affords the indicated products:

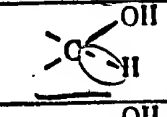
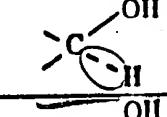
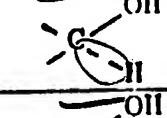
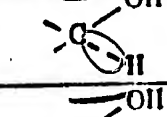
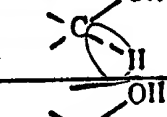
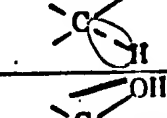
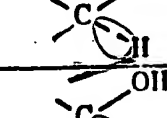
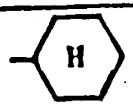
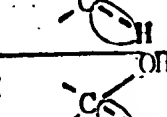
STARTING MATERIAL	PRODUCT
cortisone	17α-hydroxyandrost-4-en-3,11-dione-17β-carboxylic acid
chloroprednisone	6α-chloro-17α-hydroxyandrosta-1,4-dien-3,11-dione-17β-carboxylic acid
flumethasone	6α,9α-difluoro-11β,17α-dihydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid
fluprednisolone	6α-fluoro-11β,17α-dihydroxy-androsta-1,4-dien-3-one-17β-carboxylic acid
meprednisone	17α-hydroxy-16β-methylandrosta-1,4-dien-3,11-dione-17β-carboxylic acid
methyl prednisolone	11β,17α-dihydroxy-6α-methyl-androsta-1,4-dien-3-one-17β-carboxylic acid

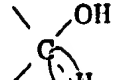
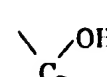
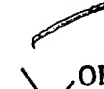
STARTING MATERIAL	PRODUCT
paramethasone	6α-fluoro-11β,17α-dihydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid
prednisolone	11β,17α-dihydroxyandrosta-1,4-dien-3-one-17β-carboxylic acid
prednisone	17α-hydroxyandrosta-1,4-dien-3,11-dione-17β-carboxylic acid
triamcinolone	9α-fluoro-11β,16α,17α-trihydroxy-androsta-1,4-dien-3-one-17β-carboxylic acid

EXAMPLE 6A

Following the general procedure of Example 2 and substituting therein the appropriate reactants affords the following novel intermediates of the present invention:



Compound No.	R_3	R_3	R_4	R_5	Z	Δ	m.p.
6A-1	$CH_2C_6H_5$	H	H	H		4	183-184°C (ethanol)
6A-2	C_2H_5	H	F	H		4	190-191°C (THF/hexane)
6A-3	C_2H_5	β-CH_3	F	H		1,4	128-129°C (THF/hexane)
6A-4	C_2H_5	α-CH_3	F	H		1,4	143-144.5°C (THF/hexane)
6A-5	iso-C_3H_7	α-CH_3	F	H		1,4	154.5-156°C (THF/hexane)
6A-6	iso-C_4H_9	H	H	H		4	125-126°C (THF/hexane)
6A-7	iso-C_3H_7	β-CH_3	F	H		1,4	171.5-172.5°C (THF/hexane)
6A-8	n-C_3H_7	H	H	H		4	156-157°C (THF/hexane)
6A-9	n-C_3H_7	α-CH_3	F	H		1,4	157-158°C (THF/hexane)
6A-10		H	H	H		4	156-157.5°C (ether/hexane)
6A-11	CH_3	α-CH_3	F	H		1,4	180-182°C (ethyl acetate)

Compound No.	R_2	R_3	R_4	R_5	Z	Δ	m.p.
6A-12	$n\text{-}C_5H_{11}$	$\alpha\text{-}CH_3$	F	H		1,4	138.5-139.5°C (THF/hexane)
6A-13	C_2H_5	$\alpha\text{-}CH_3$	F	F		1,4	157-158°C (decomp.) (THF/hexane)
6A-14	C_6H_5	$\alpha\text{-}CH_3$	F	H		1,4	246-248°C (THF/hexane)
6A-15	CH_2CH_2Cl	$\alpha\text{-}CH_3$	F	H		4	93-94°C (THF/hexane)

Compounds 6A-1 to 6A-15 above can be named as follows:

6A-1: 17α-benzyloxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid

6A-2: 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid

6A-3: 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-4: 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-5: 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-6: 11β-hydroxy-17α-isobutoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid

6A-7: 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-8: 11β-hydroxy-17α-propoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid

6A-9: 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-10: 17α-cyclohexyloxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid

6A-11: 9α-fluoro-11β-hydroxy- 17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-12: 9α-fluoro-11β-hydroxy-16α-methyl-17α-n-pentyloxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-13: 17α-ethoxycarbonyloxy-6α,9α-difluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

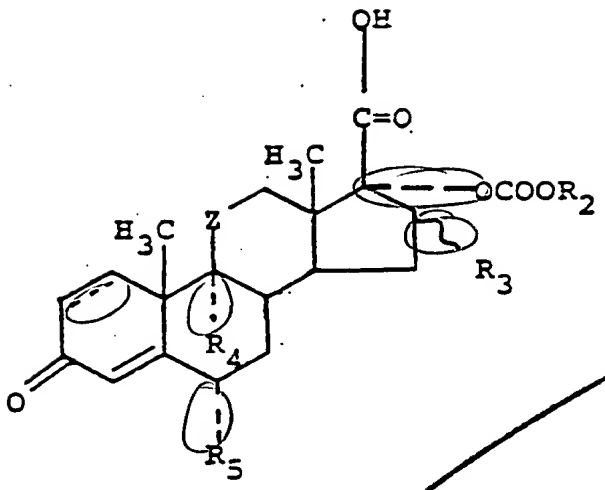
6A-14: 9α-fluoro-11β-hydroxy-16α-methyl-17α-phenoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

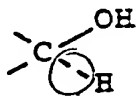
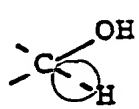
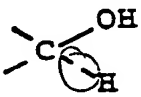
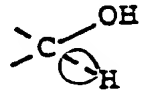
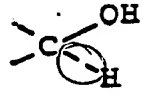
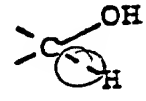
6A-15: 17α-(2-chloroethoxycarbonyloxy)-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

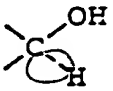
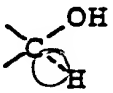
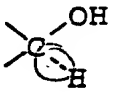
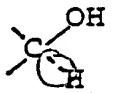
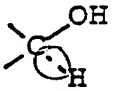
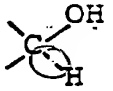
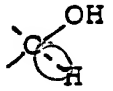
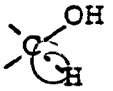
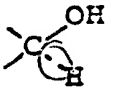
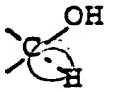
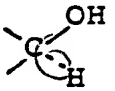
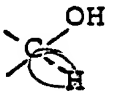
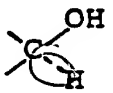
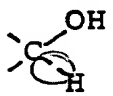
EXAMPLE 6B

Following the general procedure of Example 2 and substituting therein the appropriate reactants affords the following novel intermediates of the present invention:

TO770X



Compound No.	R_2	R_3	R_4	R_5	(Z)	Δ
6B-1	C_2H_5	H	H	H	>C = O	4
6B-2	CH_3	H	H	H	>C = O	4
6B-3	CH_3	H	F	H		4
6B-4	C_2H_5	α-CH_3	F	F		1,4
6B-5	C_2H_5	H	H	F		1,4
6B-6	C_2H_5	β-CH_3	H	H	>C = O	1,4
6B-7	CH_2CCl_3	H	H	H		4
6B-8	C_2H_5	α-CH_3	H	F		1,4
6B-9	C_2H_5	H	H	H		1,4
6B-10	C_2H_5	H	H	H	>C = O	1,4

Compound No.	R_2	R_3	R_4	R_5	Z	Δ
6B-11	C_2H_5	α-$OCOOC_2H_5$	F	H		1,4
6B-12	CH_2Cl	α-CH_3	F	H		1,4
6B-13	CH_2CH_2Cl	α-CH_3	F	H		1,4
6B-14	C_2H_5	H	H	Cl	C = O	1,4
6B-15	C_6H_5	H	H	H		4
6B-16		H	H	H		4
6B-17		H	H	H		4
6B-18	$CH=CH_2$	H	H	H		4
6B-19	CH_2OCH_3	H	H	H		4
6B-20	CH_2SCH_3	H	H	H		4
6B-21	$CH_2CH_2NHCOCH_3$	H	H	H		4
6B-22	$CH_2CH_2OCOCH_3$	H	H	H		4
6B-23	C_2H_5	H	H	CH_3		1,4
6B-24	$CH_2SO_2CH_3$*	H	H	H		4
6B-25	CH_2SOCH_3*	H	H	H		4

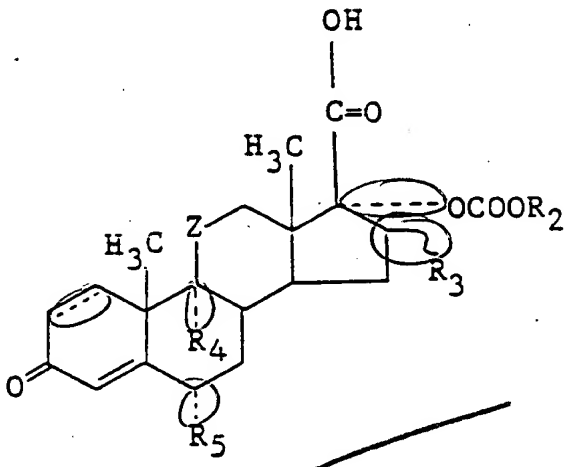
*prepared from 6B-20 by subsequent reaction with m-chloroperbenzoic acid.

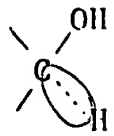
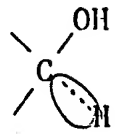
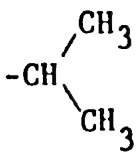
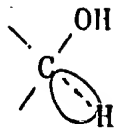
Cl

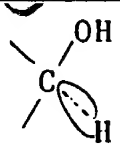
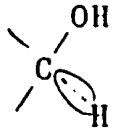
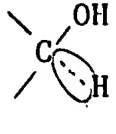
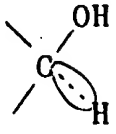
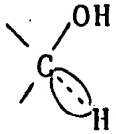
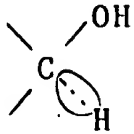
EXAMPLE 6C

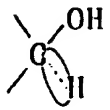
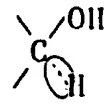
P Following the general procedure of Example 2 and substituting therein the appropriate reactants affords the following novel intermediates of the present invention:

70790X



Compound No.	R_2	R_3	R_4	R_5	Z	Δ	m.p.
6C-1	$-CH_2CH=CH_2$	α-CH_3	F	H		1,4	227 - 229°C (THF/hexane)
6C-2	$-CH_2CH_2CH_3$	α-CH_3	F	F		1,4	148 - 155°C (decomp.) (ethanol/water)
6C-3		α-CH_3	F	F		1,4	157-159°C (ethanol/water)

Compound No.	R_2	R_3	R_4	R_5	Z	Δ	m.p.
6C-4	$-C_2H_5$	α-CH_3	H	F		1,4	105-108°C (THF/n-hexane)
6C-5	$-(CH_2)_2CH_3$	α-CH_3	H	F		1,4	150-152°C (THF/n-hexane)
6C-6	$-CH(CH_3)_2$	α-CH_3	H	F		1,4	124-127°C (THF/n-hexane)
6C-7	$-CH_3$	H	H	H		1,4	178-180°C (THF/n-hexane)
6C-8	$-CH_3$	α-CH_3	H	F		1,4	182-183°C (THF/n-hexane)
6C-9	$-C_2H_5$	H	H	H		1,4	153-156°C (THF/n-hexane)

Compound No.	R_2	R_3	R_4	R_5	Z	Δ	mp
6C-10	$-CH_3$	β-CH_3	F	H		1,4	186-188 (decomposition) (THF/n-hexane)
6C-11	$-CH_2CH_2CH_3$	β-CH_3	F	H		1,4	143-144.5°C (THF/n-hexane)

The foregoing compounds can be named as follows:

6C-1: 17α-allyloxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-2: 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-3: 6α,9α-difluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-4: 17α-ethoxycarbonyloxy-6α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-5: 6α-fluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-6: 6α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-7: 11β-hydroxy-17α-methoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-8: 6α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-9: 17α-ethoxycarbonyloxy-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-10: 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy- 16β-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

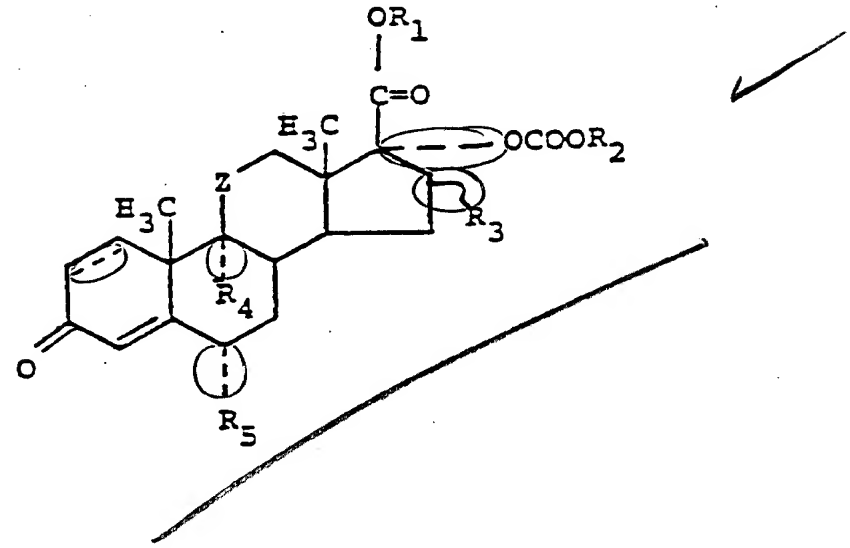
6C-11: 9α-fluoro-11β-hydroxy-16β-methyl-17α-n-propoxy-carbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

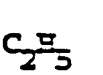
Cl
P

EXAMPLE 7A

Following the general procedure of Example 3 and substituting therein the appropriate reactants affords the following compounds:

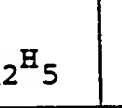
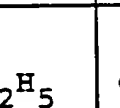
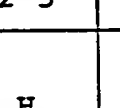
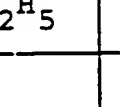
TO890X



Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ	m.p.
7A-1	CH_2Cl	C_2H_5	H	F	H		4	228-229°C (THF/hexane)
7A-2	CH_2Cl	C_2H_5	β-CH_3	F	H		1,4	220-221°C (THF/hexane)
7A-3	CH_2Cl	C_2H_5	α-CH_3	F	H		1,4	230-235°C (THF/hexane)
7A-4	CH_2Cl	C_2H_5	H	H	H		1,4	220.5-223.5°C (THF/hexane)
7A-5	CH_2Cl	iso-C_3H_7	H	H	H		1,4	197-198°C (THF/hexane)
7A-6	CH_2Cl	C_2H_5	H	F	H		1,4	245-248°C (THF/hexane)
7A-7	CH_2Cl	iso-C_3H_7	α-CH_3	F	H		1,4	184.5-186°C (THF/hexane)
7A-8	CH_2Cl	iso-C_3H_7	β-CH_3	F	H		1,4	174-175.5°C (THF)
7A-9	CH_2Cl	iso-C_4H_9	H	H	H		4	140-141°C (THF/isopropyl ether)
7A-10	CH_2Cl		H	H	H		4	148-150°C (isoprcpyl ether hexane)
7A-11	CH_2Cl	n-C_3H_7	H	H	H		4	181-182°C (THF/hexane)
7A-12	CH_2Cl	n-C_3H_7	α-CH_3	F	H		1,4	176-176.5°C (THF/hexane)
7A-13	CH_3	iso-C_3H_7	H	H	H		4	211.5-213.5°C (THF/hexane)
7A-14	$CH_2OC_2H_5$	iso-C_3H_7	H	H	H		4	137-138°C (THF/hexane)
7A-15	CH_2Cl	CH_2	H	H	H		4	182-183°C (ethanol)

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ	m.p.
7A-16*	CH_3 | $CHCl$	iso-C_3H_7	H	H	H		4	181-182.5°C (THF/hexane)
	CH_3 | $CHCl$	iso-C_3H_7	H	H	H		4	199-200°C (THF/hexane)
7A-17	$CH_2CO_2C_2H_5$	iso-C_3H_7	H	H	H		4	73-74°C (isopropyl ether)
7A-18*	CH_3 | $CHCl$	iso-C_3H_7	β-CH_3	F	H		1,4	167.5-169°C (THF/hexane)
	CH_3 | $CHCl$	iso-C_3H_7	β-CH_3	F	H		1,4	163-164°C (THF/hexane)
7A-19	CH_2Cl	iso-C_3H_7	β-CH_3	F	H		1,4	200-201°C (THF/iso-propyl ether)
7A-20	CH_2Cl	C_2H_5	α-CH_3	F	H		1,4	138-140°C (THF/iso-propyl ether)
7A-21	CH_2Cl	CH_3	α-CH_3	F	H		1,4	260-263°C (THF/hexane)
7A-22	CH_2F	iso-C_3H_7	H	H	H		4	207.5-210°C (THF/hexane)
7A-23	CH_2Cl	n-C_5H_{11}	α-CH_3	F	H		1,4	176-177°C (THF/hexane)
7A-24	CH_2Cl	C_2H_5	α-$C(=O)OC_2H_5$	H	F		1,4	153-154°C (THF/hexane)
7A-25	CH_2F	C_2H_5	α-CH_3	F	H		1,4	239-240.5°C (THF/hexane)
7A-26	CH_2OCOCH_3	C_2H_5	H	H	H		4	NMR ($CDCl_3$) δ5.76(s,2, OCH_2O), 2.01 (s,3, $COCH_3$)

* diastereomers

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ	m.p.
7A-27	CH_2Cl	C_2H_5	α-CH_3	F	F		1,4	195-197°C (THF/hexane)
7A-28	CH_2CH_2Cl	C_2H_5	α-CH_3	F	H		1,4	243-245°C (THF/hexane)
7A-29	CH_3	C_2H_5	α-CH_3	F	H		1,4	258.5-262.5°C (THF/hexane)
7A-30	CH_2CH_2Cl	iso-C_3H_7	H	H	H		4	188.5-189.5°C (THF/hexane)

The foregoing compounds can be named as follows:

7A-1: chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxyandrost-4-en-3-one-17β-carboxylate

7A-2: chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-3: chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-4: chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxy-androsta-1,4-dien-3-one-17β-carboxylate

7A-5: chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androsta-1,4-dien-3-one-17β-carboxylate

7A-6: chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylate

7A-7: chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-8: chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxy-carbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-9: chloromethyl 11β-hydroxy-17α-isobutoxycarbonyloxy-androst-4-en-3-one-17β-carboxylate

7A-10: chloromethyl 17α-cyclohexyloxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate

7A-11: chloromethyl 11β-hydroxy-17α-propoxycarbonyloxy-androst-4-en-3-one-17β-carboxylate

7A-12: chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7A-13: methyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β- carboxylate

7A-14: ethoxymethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate

7A-15: chloromethyl 17α-benzyloxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate

7A-16: 1-chloroethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androst-4-en-3-one-17β-carboxylate

7A-17: ethoxycarbonylmethyl 11β-hydroxy-17α-isopropoxy-carbonyloxyandrost-4-en-3-one-17β-carboxylate

PO 60,62 L 62 7A-18: 1-chloroethyl 9α-fluoro-11β-hydroxy-17α isopropoxycarbonyloxy-16β-methylandrosta-1,4 dien-3-one-17β-carboxylate

PO 60 62 5 7A-19: chloromethyl 9α-fluoro-17α-isopropoxycarbonyloxy 16β-methylandrosta-1,4-dien-3,11-dione-17 carboxylate

PO 60 L 7A-20: chloromethyl 9α-fluoro-17α-isopropoxycarbonyloxy 16α-methylandrosta-1,4-dien-3,11-dione-17 carboxylate

PO 60 L 10 62 62 7A-21: chloromethyl 9α-fluoro-11β-hydroxy-17α methoxycarbonyloxy-16α-methylandrosta-1,4-dien 3-one-17β-carboxylate

PO 62,60 L 7A-22: fluoromethyl 11β-hydroxy-17α-isopropoxycarbonyl-oxyandrost-4-en-3-one-17β-carboxylate

PO 60 L 15 62 62 7A-23: chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl 17α-pentyloxycarbonyloxyandrosta-1,4-dien-3-one 17β-carboxylate

PO 60 62 20 7A-24: chloromethyl 16α,17α-di(ethoxycarbonyloxy)-6α fluoro-11β-hydroxyandrosta-1,4-dien-3-one-17β carboxylate

PO 60,62 L L 7A-25: fluoromethyl 17α-ethoxycarbonyloxy-9α-fluoro- 11β hydroxy-16α-methylandrosta-1,4-dien-3-one-17β carboxylate

PO 60,62 25 L 7A-26: acetoxymethyl 17α-ethoxycarbonyloxy-11β-hydroxy-androst-4-en-3-one-17β-carboxylate

PO 60 62,60 7A-27: chloromethyl 17α-ethoxycarbonyloxy-6α,9α-difluoro 11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β carboxylate

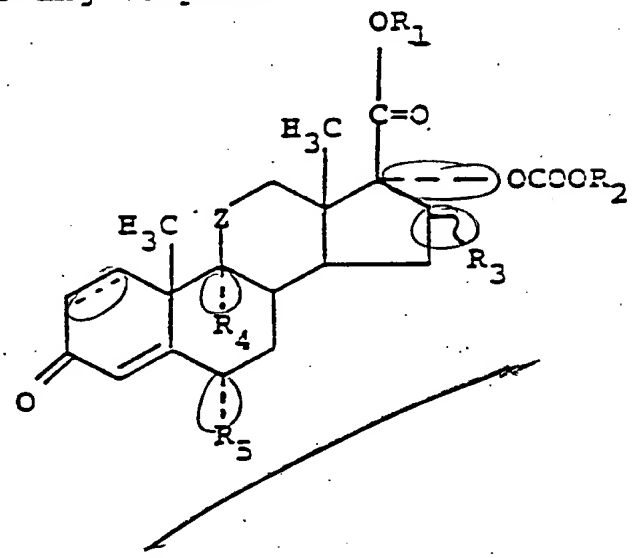
PO 60,62 L L 7A-28: 2-chloroethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β hydroxy-16α-methylandrosta-1,4-dien-3-one-17β carboxylate

PO 60,62 L L 7A-29: methyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy 16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

PO 62,60 L 7A-30: 2-chloroethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androst-4-en-3-one-17β-carboxylate

EXAMPLE 7B

Following the general procedure of Examples 3 or 4 and substituting therein the appropriate reactants affords the following compounds:



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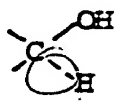
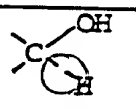
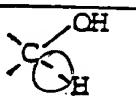
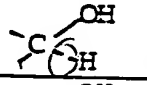
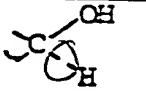
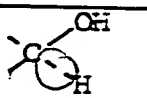
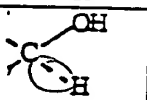
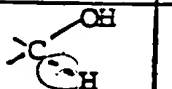
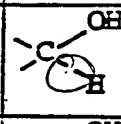
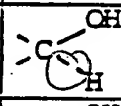
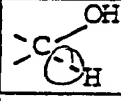
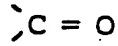
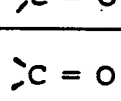
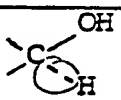
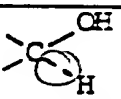
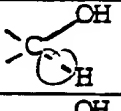
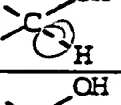
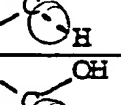
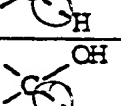
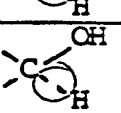
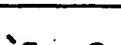
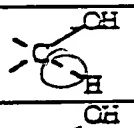
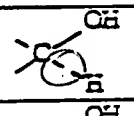
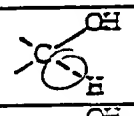
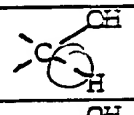
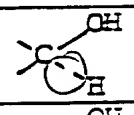
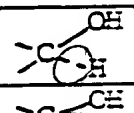
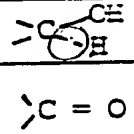
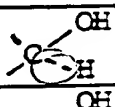
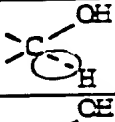
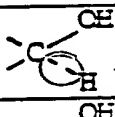
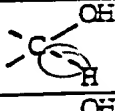
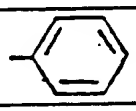
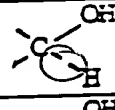
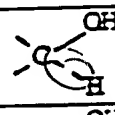
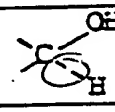
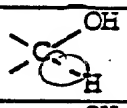
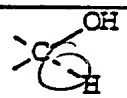
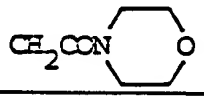
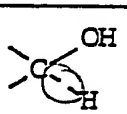
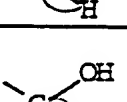
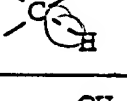
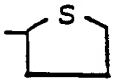
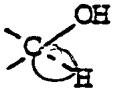
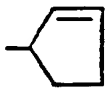
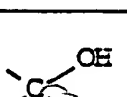
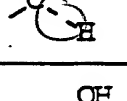
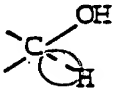
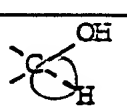
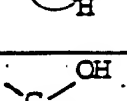
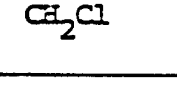
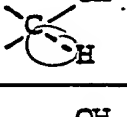
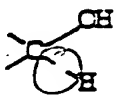
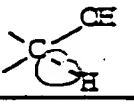
Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ
7B-1	C_2H_5	C_2H_5	H	H	H		4
7B-2	C_4H_9	$CH_2C_6H_5$	H	H	H		4
7B-3	$CH_2COOC_2H_5$	C_2H_5	H	H	H		4
7B-4	CH_2OCOCH_3	C_2H_5	H	H	H		4
7B-5	CH_2Cl	C_6H_5	H	H	H		4
7B-6	CH_2Cl		H	H	H		4
7B-7	CH_2Cl	CH_2SCH_3	H	H	H		4
7B-8	C_4H_9	C_2H_5	H	H	H	>C = O	4
7B-9	CH_2Cl	CH_3	H	H	H	>C = O	4
7B-10	CH_2Cl	C_2H_5	H	H	H	>C = O	4
7B-11	CH_2SCH_3	C_2H_5	H	H	H	>C = O	4
7B-12	$CH_2SO_2CH_3$	C_2H_5	H	H	H	>C = O	4
7B-13	CH_2SOCH_3	C_2H_5	H	H	H	>C = O	4
7B-14	CH_2Cl	CH_3	H	F	H		4
7B-15	CH_2SCH_3	C_2H_5	H	F	H		4

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ
7B-16	$CH_2SO_2CH_3$	C_2H_5	H	F	H		4
7B-17	CH_2SCH_3	C_2H_5	β-CH_3	F	H		1,4
7B-18	$CH_2SO_2CH_3$	C_2H_5	β-CH_3	F	H		1,4
7B-19	CH_2Cl	C_2H_5	H	H	Cl		1,4
7B-20	CH_2SCH_3	C_2H_5	H	H	Cl		1,4
7B-21	$CH_2SO_2CH_3$	C_2H_5	H	H	Cl		1,4
7B-22	CH_2SCH_3	C_2H_5	α-CH_3	F	H		1,4
7B-23	$CH_2SO_2CH_3$	C_2H_5	α-CH_3	F	H		1,4
7B-24	CH_2Cl	C_2H_5	α-CH_3	F	F		1,4
7B-25	CH_2SCH_3	C_2H_5	α-CH_3	F	F		1,4
7B-26	$CH_2SO_2CH_3$	C_2H_5	α-CH_3	F	F		1,4
7B-27	CH_2Cl	C_2H_5	H	H	F		1,4
7B-28	CH_2SCH_3	C_2H_5	H	H	F		1,4
7B-29	$CH_2SO_2CH_3$	C_2H_5	H	H	F		1,4
7B-30	CH_2Cl	C_2H_5	β-CH_3	H	H		1,4
7B-31	CH_2SCH_3	C_2H_5	β-CH_3	H	H		1,4
7B-32	$CH_2SO_2CH_3$	C_2H_5	β-CH_3	H	H		1,4

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ
7B-33	CH_2Cl	C_2H_5	H	H	CH_3		1,4
7B-34	CH_2SCH_3	C_2H_5	H	H	CH_3		1,4
7B-35	$CH_2SO_2CH_3$	C_2H_5	H	H	CH_3		1,4
7B-36	CH_2Cl	C_2H_5	α-CH_3	H	F		1,4
7B-37	CH_2SCH_3	C_2H_5	α-CH_3	H	F		1,4
7B-38	$CH_2SO_2CH_3$	C_2H_5	α-CH_3	H	F		1,4
7B-39	CH_2SCH_3	C_2H_5	H	H	H		1,4
7B-40	$CH_2SO_2CH_3$	C_2H_5	H	H	H		1,4
7B-41	CH_2Cl	C_2H_5	H	H	H	>C = O	1,4
7B-42	CH_2SCH_3	C_2H_5	H	H	H	>C = O	1,4
7B-43	$CH_2SO_2CH_3$	C_2H_5	H	H	H	>C = O	1,4
7B-44	CH_2Cl	C_2H_5	α-$OCOOC_2H_5$	F	H		1,4
7B-45	CH_2SCH_3	C_2H_5	α-$OCOOC_2H_5$	F	H		1,4
7B-46	$CH_2SO_2CH_3$	C_2H_5	α-$OCOOC_2H_5$	F	H		1,4
7B-47	CH_2Cl	C_2H_5	α-OH	H	F		1,4
7B-48	CH_2Cl		α-CH_3	F	H		1,4
7B-49	CH_2Cl	CH_2CH_2Cl	α-CH_3	F	H		1,4
7B-50	CH_3	CH_2Cl	α-CH_3	F	H		1,4

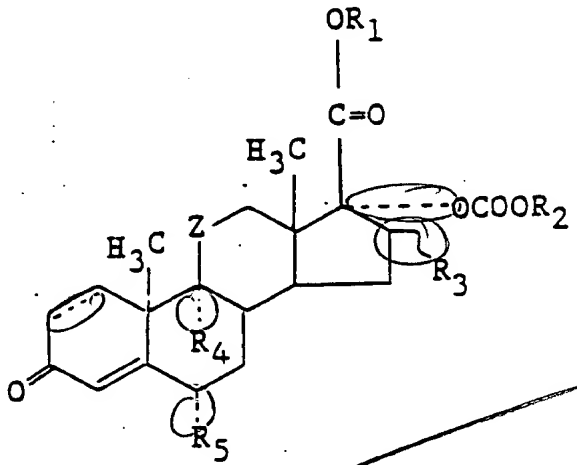
Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ
7B-51	C_4H_9	CH_2CCl_3	H	H	H		4
7B-52	$CH_2CON(C_2H_5)_2$	C_2H_5	H	H	H		4
7B-53		CH_3	H	H	H		4
7B-54	C_6H_5	C_2H_5	H	H	H		4
7B-55	$CH_2C_6H_5$	CH_3	H	H	H		4
7B-56		C_2H_5	H	H	H		4
7B-57	CH_2Cl		H	H	H		4
7B-58	CH_2Cl	$CH=CH_2$	H	H	H		4
7B-59	CH_2Cl	CH_2OCH_3	H	H	H		4
7B-60	CH_2Cl	$CH_2CH_2NHCOOCH_3$	H	H	H		4
7B-61	CH_2Cl	$CH_2CH_2OCOOCH_3$	H	H	H		4
7B-62		C_2H_5	H	H	H		4

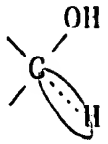
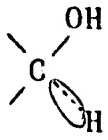
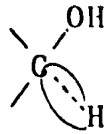
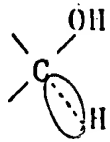
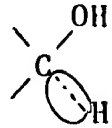
Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ
7B-63	CH_2Cl	$CH_2SO_2CH_3$*	H	H	H		4
7B-64	CH_2Cl	CH_2SOCH_3*	H	H	H		4

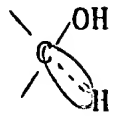
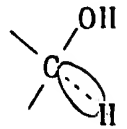
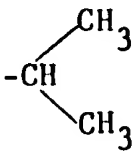
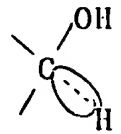
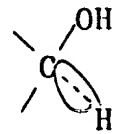
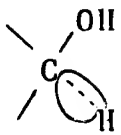
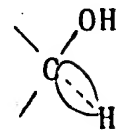
* prepared from Example 6B-24 and 6B-25 respectively by reaction with $ClCH_2I$, or from Example 7B-7 by reaction with m-chloroperbenzoic acid.

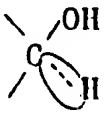
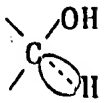
EXAMPLE 7C

Following the general procedure of Example 3 and substituting therein the appropriate reactants affords the following compounds:



Compound	R_1	R_2	R_3	R_4	R_5	Z	Δ	m.p.
7C-1	$-CH_2Cl$	$-CH(CH_3)_2$	α-CH_3	F	F		1,4	222 - 224°C (THF/hexane)
7C-2	$-CH_2Cl$	$-CH_2CH_2CH_3$	α-CH_3	F	F		1,4	180.5 - 181.5°C (THF/hexane)
7C-3	$-CH_2F$	$-CH_2CH_2CH_3$	α-CH_3	F	H		1,4	165 - 165.5°C (THF/hexane)
7C-4	$-CH_2CH_2Cl$	$-CH(CH_3)_2$	H	H	H		1,4	188.5 - 189.5°C (THF/hexane)
7C-5	$-CH_3$	$-CH_2CH_2Cl$	α-CH_3	F	H		1,4	223 - 227°C (isopropanol)

Compound No.	R_1	R_2	R_3	R_4	R_5	Z		m.p.
7C-6	$-CH_2Cl$	$-C_2H_5$	α-CH_3	H	F		1,4	153.5-154.5°C (THF/n-hexane)
7C-7	$-CH_2Cl$	$-(CH_2)_2CH_3$	α-CH_3	H	F		1,4	98.5-99.5°C (ethyl acetate/n-hexane)
7C-8	$-CH_2Cl$		α-CH_3	H	F		1,4	124.5-126°C (ethyl acetate/n-hexane)
7C-9	$-CH_2Cl$	$-(CH_2)_2CH_3$	H	H	H		1,4	180.5-181.5°C (THF/n-hexane)
7C-10	$-CH_2Cl$	$-CH_3$	H	H	H		1,4	235-237°C (THF/n-hexane)
7C-11	$-CH_2Cl$	$-CH_3$	α-CH_3	H	F		1,4	244.5-245.5°C (THF/n-hexane)

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ	mp
7C-12	$-CH_2Cl$	$-CH_3$	β-CH_3	F	H		1,4	236-236.5°C (THF/n-hexane)
7C-13	$-CH_2Cl$	$-CH_2CH_2CH_3$	β-CH_3	F	H		1,4	183.5-184°C (THF/n-hexane)

The foregoing compounds can be named as follows:

7C-1: chloromethyl 6α,9α-difluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7C-2: chloromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7C-3: fluoromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7C-4: 2-chloroethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androsta-1,4-dien-3-one-17β-carboxylate

7C-5: methyl 17α-(2-chloroethoxy)carbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7C-6: chloromethyl 17α-ethoxycarbonyloxy-6α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7C-7: chloromethyl 6α-fluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7C-8: chloromethyl 6α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

PO 62, 60 7C-9: chloromethyl 11β-hydroxy-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate
62

PO 62, 60 7C-10: chloromethyl 11β-hydroxy-17α-methoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate
5
62

PO 60, 62 7C-11: chloromethyl 6α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate
L
62

PO 60 10 62 7C-12: chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate
L

PO 60, 62 7C-13: chloromethyl 9α-fluoro-11β-hydroxy-16β-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate
L
62 15

Cl
P

EXAMPLE 8

An equivalent quantity of 11β,17α-dihydroxy-androst-4-en-3-one-17β-carboxylic acid is substituted for the 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid starting material employed in Example 3, and the procedure of the first paragraph of that example is substantially repeated. There are thus obtained, as the intermediate salt, sodium 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate, and, as the final product, chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate, melting at 184-186°C (recrystallization from tetrahydrofuran-ether-hexane).

Cl
P

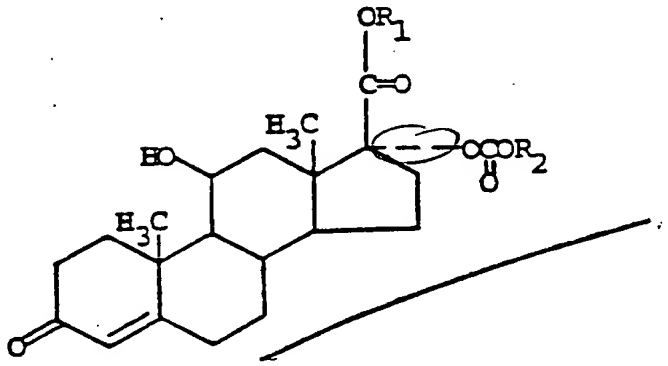
EXAMPLE 9

An equivalent quantity of 11β,17α-dihydroxy-androst-4-en-3-one-17β-carboxylic acid is substituted for the 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid starting material employed in Example 4, and the procedure of the first paragraph of that example is substantially repeated. There are thus obtained, as the intermediate salt, sodium 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate, and, as the final product, methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate.

Substitution of an equivalent quantity of methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate for the methylthiomethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate used in the second paragraph of Example 4 and substantial repetition of the procedure there detailed affords methylsulfonylmethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate.

EXAMPLE 10A

The procedure of each paragraph of Example 2 is substantially repeated, substituting an equivalent quantity of each of the following starting materials for the steroids employed therein: chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate; and methylthiomethyl 11β, 17α-dihydroxyandrost-4-en-3-one-17β-carboxylate. The following soft anti-inflammatory agents of formula (I) are obtained:

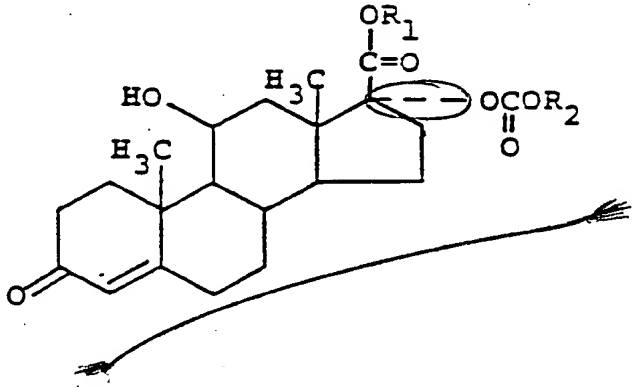


Compound No.	R_1	R_2	m.p.
10A-1	CH_2Cl	CH_3	171-173°C
10A-2	CH_2Cl	C_2H_5	197-200°C(THF/hexane)
10A-3	CH_2SCH_3	C_2H_5	137.5-138°C(ether/hexane)
10A-4	CH_2Cl	C_4H_9	99.5-102°C(THF/hexane)
10A-5	CH_2Cl	iso-C_3H_7	183.5-184.5°C(THF/hexane)
10A-6 *	CH_2Cl	iso-C_4H_9	140-141°C(THF/isopropyl ether)

*utilizing isobutyl chloroformate as the alkyl chloroformate reactant

EXAMPLE 10B

The procedure of each paragraph of Example 2 is substantially repeated, substituting an equivalent quantity of each of the following starting materials for the steroids employed therein: methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate; and methylsulfonylmethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate. The following soft anti-inflammatory agents of formula (I) are obtained.

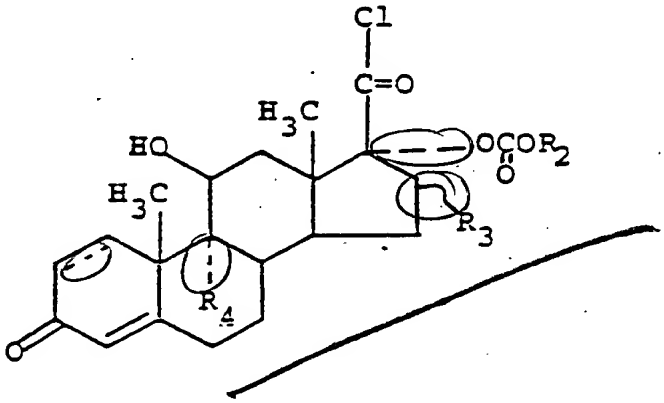


Compound No.	R_1	R_2
10B-1	CH_2SCH_3	CH_3
10B-2	CH_2SCH_3	C_4H_9
10B-3	CH_2SCH_3	$i\text{-}C_3H_7$
10B-4	$CH_2SO_2CH_3$	CH_3
10B-5	$CH_2SO_2CH_3$	C_2H_5
10B-6	$CH_2SO_2CH_3$	C_4H_9
10B-7	$CH_2SO_2CH_3$	$i\text{-}C_3H_7$

Other representative species, e.g. compounds of Examples 7A and 7B, can likewise be prepared according to the procedures of Examples 8 through 10.

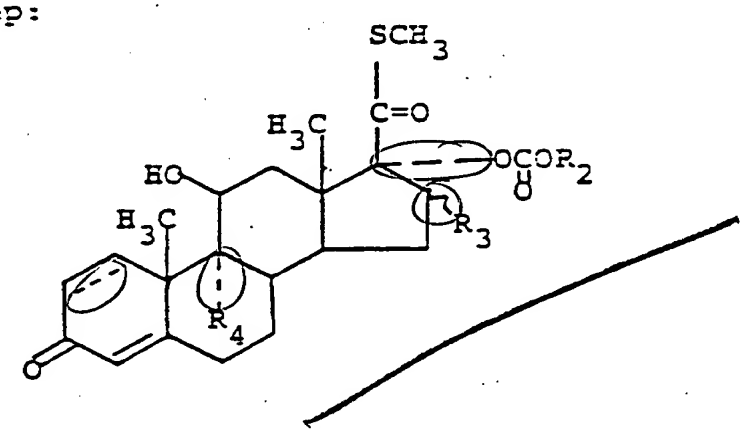
EXAMPLE 11

The products of Example 2 and Example 6A-4 are each allowed to react, first with diethylchlorophosphate and then with CH_3SNa in chloroform for approximately 6 hours. The following intermediates are obtained in the first step:



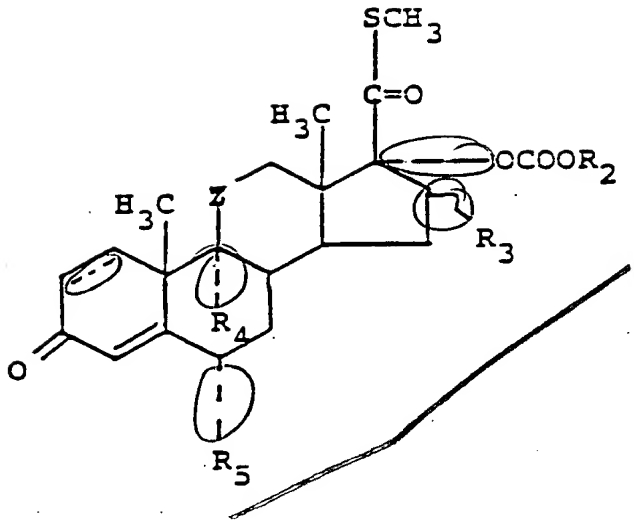
R_2	R_3	R_4	Δ
CH_3	H	H	4
C_2H_5	H	H	4
C_4H_9	H	H	4
i-C_3H_7	H	H	4
C_2H_5	α-CH_3	F	1,4

and the following compounds of formula (I) are obtained in the second step:



R_2	R_3	R_4	Δ
CH_3	H	H	4
C_2H_5	H	H	4
C_4H_9	H	H	4
i-C_3H_7	H	H	4
C_2H_5	α-CH_3	F	1,4

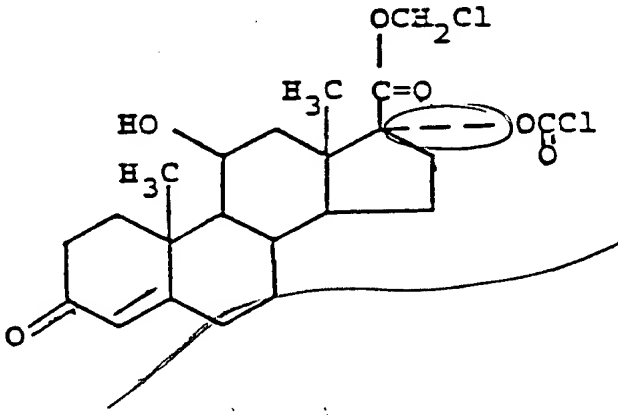
When the remaining products of Example 6A and those of Example 6B are treated according to the above procedure, the corresponding compounds of the formula



wherein the various structural parameters represented by R_2, R_3, R_4, R_5, Z and the dotted line are identical to those of compounds 6A1-6A3, 6A5-6A11, and 6B1-6B25 of Examples 6A and 6B are obtained.

EXAMPLE 12

Chloromethyl 11β, 17α-dihydroxyandrost-4-ene-3-one-17β-carboxylate (0.01 mol) is dissolved in toluene (100 milliliters) and the solution is cooled to approximately 0°C. Phosgene is then bubbled into the solution, while maintaining the reaction mixture at low temperature, until the reaction is complete (approximately 2 hours). The solvent and excess phosgene are removed by evaporation to leave the crude 17α-chlorocarbonyloxy compound of the formula



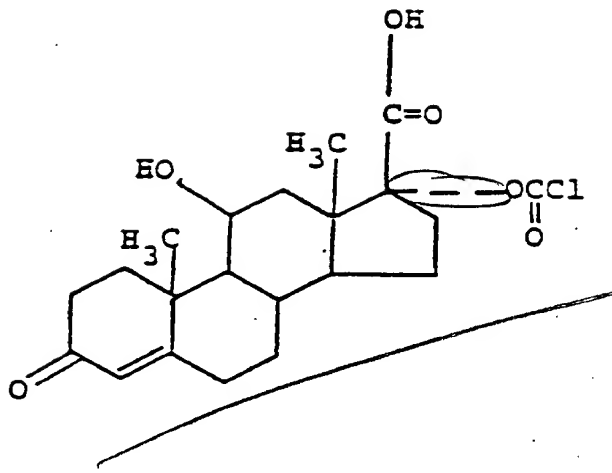
The intermediate (0.01 mol) obtained above is then combined with ethanol (0.02 mol) containing 2,6-dimethylpyridine (0.01 mol) and allowed to react at room temperature for 6 hours. At the end of that time, the desired chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate is isolated from the reaction mixture. The compound melts at 197-200°C, after crystallization.

Substitution of an equivalent quantity of methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate for the chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate used above and substantial repetition of the foregoing procedure affords methylthiomethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 133-136°C, after crystallization. That compound can then, if desired, be converted to the corresponding sulfonyl or sulfinyl compound as described in Example 4.

Other representative species, e.g., the compounds of Example 3, paragraphs 1, 3, 4 and 5, and the compounds of Examples 7A and 7B can be prepared in like manner from reaction of the corresponding 17α-hydroxy 17β-carboxylates with the appropriate alcohols, including, when appropriate, subsequent treatment with m-chloroperoxybenzoic acid as in Example 4.

EXAMPLE 13

The procedure of the first paragraph of Example 12 is repeated, except that an equivalent quantity of 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid is used in place of the chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate. The crude intermediate thus obtained has the formula



That intermediate is then subjected to the procedure of the second paragraph of Example 12, to afford 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid, identical to the product of Example 2, paragraph 2.

The other compounds of Examples 2, 6A and 6B can be prepared using the same general procedure.

EXAMPLE 14

Chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate (0.02 mol) is combined with diethylcarbonate (0.2 mol) containing 20 mg of p-toluenesulfonic acid. The reaction mixture is maintained at room temperature for 4 hours, then heated to about 80 to 85°C; the remaining ethanol which forms is removed by distillation under reduced pressure. Obtained as the residue is crude chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 197-200°C, after crystallization.

Substitution of an equivalent quantity of methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate for the chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate used above and substantial repetition of the foregoing procedure affords methylthiomethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-

4-en-3-one-17β-carboxylate, melting at 133-136°C. That compound can then, if desired, be converted to the corresponding sulfonyl or sulfinyl compound as described in Example 4.

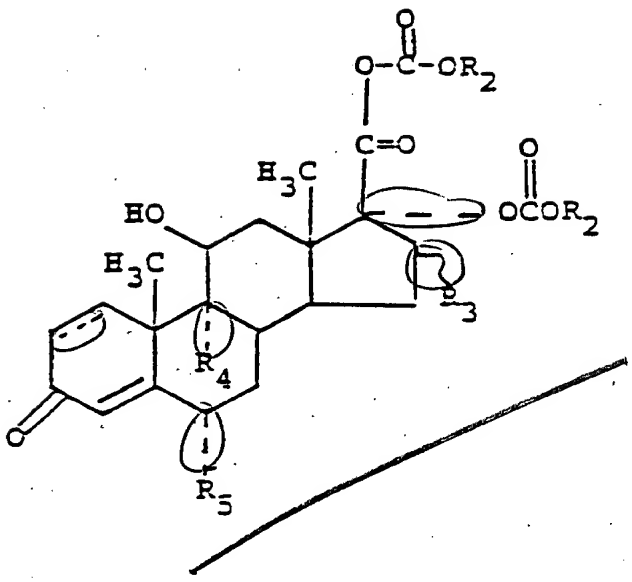
Other representative species, e.g., the compounds of Example 3, paragraphs 1, 3, 4 and 5, and the compounds of Examples 7A and 7B, can be prepared in like manner from reaction of the corresponding 17α-hydroxy-17β-carboxylates with the appropriate carbonates of the type R_2OCOR_2 (including, when appropriate, subsequent treatment with m-chloroperoxybenzoic acid as in Example 4).

EXAMPLE 15

To a solution of 8.7 grams of 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid and 9.6 milliliters of triethylamine in 100 milliliters of dry dichloromethane, is added 10 grams of ethyl chloroformate, dropwise at 0 to 5°C. The reaction mixture is gradually allowed to warm to room temperature and the insoluble material is removed by filtration. The filtrate is washed successively with 3% aqueous sodium bicarbonate, 1% hydrochloric acid, and water, then is dried over anhydrous magnesium sulfate. The solvent is concentrated under reduced pressure and the residue is crystallized to give 10.5 grams of ethoxycarbonyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 158-159°C.

EXAMPLE 16

Following the general method described in Example 15 and substituting therein the appropriate reactants affords the following additional compounds:



Compound No.	R_2	R_3	R_4	R_5	Δ	melting point
16-A	$-CH_2CH_3$	H	F	H	4	110-111°C (THF-isopropyl ether)
16-B	iso-C_3H_7	H	H	H	4	200-203°C
16-C	$-CH_2CH_2CH_3$	H	H	H	4	142-143°C (THF)

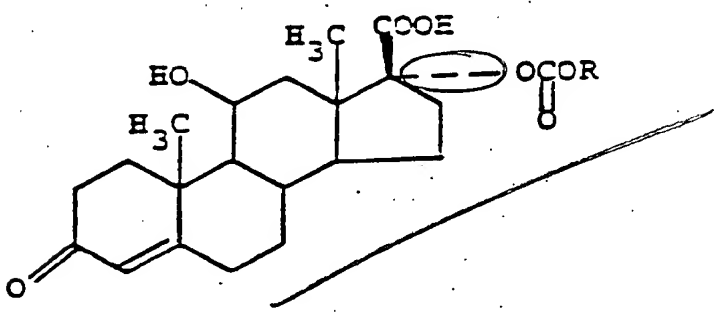
EXAMPLE 17

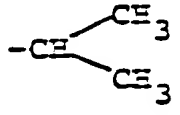
To a solution of 9.8 grams of ethoxycarbonyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate in 100 milliliters of tetrahydrofuran and 120 milliliters of ethanol are added 42 milliliters of 5% aqueous sodium bicarbonate. The mixture is stirred at room temperature for about 30 hours and adjusted to pH 2 to 3 by adding 1N hydrochloric acid. The insoluble material is isolated by filtration. Recrystallization from a mixture of tetrahydrofuran and n-hexane gives 6 grams of 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid having a melting point of 192-195°C.

The compound obtained in Example 2, first paragraph, and the compounds of Example 6A can be prepared, following the same procedure as above and substituting therein appropriate reactants.

EXAMPLE 18

Following the general method described in Example 17 and substituting therein the appropriate reactants affords the following compounds:



Compound No.	R	melting point
18-A		144.5-146.5°C (THF/hexane)
18-B	$-(CH_2)_5CH_3$	164-166°C (THF/hexane)

EXAMPLE 19

To a solution of 8.7 grams of 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid and 10 grams of triethylamine in 100 milliliters of dichloromethane, a solution of 13.2 grams of n-propyl chloroformate in 20 milliliters of dichloromethane is added dropwise over 1-1.5 hours with ice-cooling. The reaction mixture is allowed to warm to room temperature over a 2 hour period, then is washed successively with 3% aqueous sodium bicarbonate, 1N hydrochloric acid, and water and dried over anhydrous sodium sulfate. The solvent is concentrated under reduced pressure. Crystallization from a mixture of ether and n-hexane

gives 10.5 grams of propoxycarbonyl 11β-hydroxy-17α-propoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, which is dissolved in 40 milliliters of pyridine. To that solution, 300 milliliters of water are added dropwise over a 1 to 1.5 hour period. The mixture is stirred for one hour and adjusted to pH 2 to 2.5 by adding concentrated hydrochloric acid with ice-cooling. The mixture is then extracted with chloroform, washed successively with 1N hydrochloric acid and water, and then dried over sodium sulfate. The solvent is concentrated under reduced pressure, and the residue is recrystallized from a mixture of acetone and tetrahydrafuran to give 7.7 grams of 11β-hydroxy-17α-propoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid, melting at 156-157°C.

EXAMPLE 20

Following the general procedure detailed in Example 19, but utilizing the appropriate starting materials and reaction conditions, affords the remaining compounds of Example 6A.

EXAMPLE 21

Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate (2 grams) is dissolved in anhydrous dichloromethane (200 milliliters) and pyridinium chlorochromate (3.5 grams) is added at room temperature, with stirring. The resultant mixture is stirred for 24 hours, then the solvent is concentrated under reduced pressure at about 10 to 20°C. The residue is subjected to column chromatography on silica gel (Kiesel gel 60), using chloroform as an eluting solvent, followed by recrystallization from a mixture of tetrahydrofuran and

isopropyl ether to give chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-16α-methylandrosta-1,4-dien-3,11-dione-17β-carboxylate, in the yield of 1.7 grams, melting at 138-140°C.

EXAMPLE 22

By a method similar to that described in Example 21, there is obtained chloromethyl 9α-fluoro-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3,11-dione-17β-carboxylate, melting at 200-201°C.

EXAMPLE 23

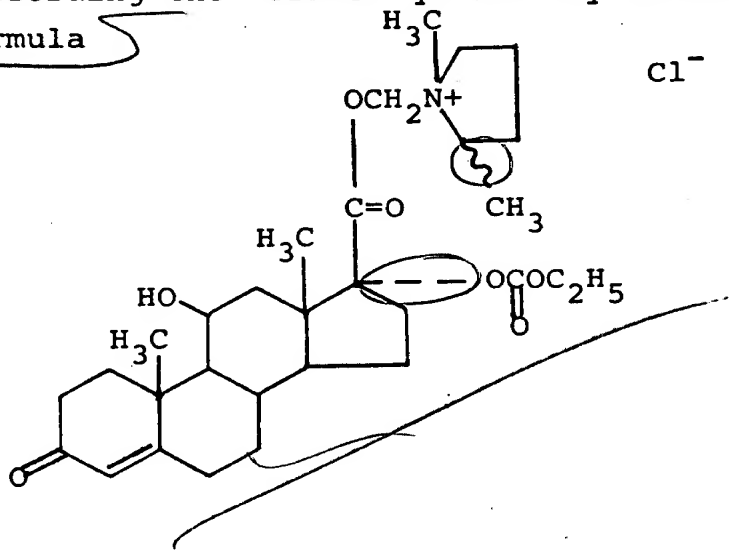
Utilizing the general procedure of Example 3, but substituting the appropriate reactants therein, affords methyl 17α-(2-chloroethoxy)carbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate. That product, after recrystallization from isopropanol, melts at 223-227°C.

EXAMPLE 24

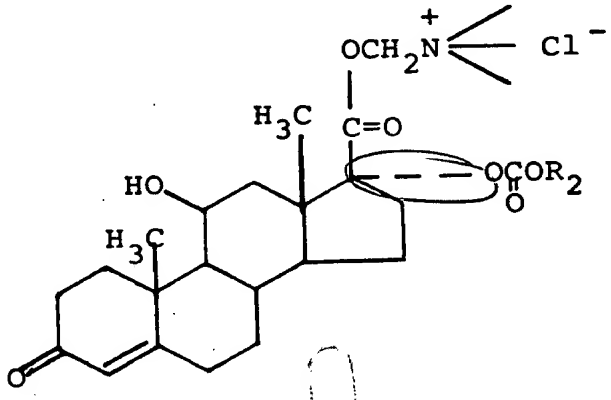
In the same general manner as in Example 3, there is obtained 2-chloroethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate. That product, after recrystallization from tetrahydrofuran-hexane, melts at 243-245°C.

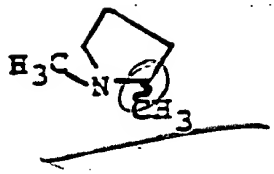
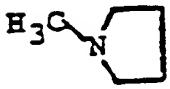
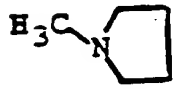
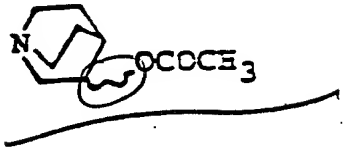
EXAMPLE 25

Chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate (0.01 mol) and 1,2-dimethylpyrrolidine (0.01 mol) are dissolved in acetonitrile (80 milliliters), and heated to the reflux temperature. The reaction mixture is maintained at that temperature, with stirring, for approximately 4 hours. About 65 ml of acetonitrile are removed; then, the mixture is cooled to room temperature and excess ethyl ether is added to cause precipitation. The precipitate is separated by filtration, washed, and dried in vacuo, thus affording the desired quaternary ammonium salt of the formula



In analogous fashion, use of the appropriate steroidal and amine starting materials in the foregoing general procedure affords the following additional quaternary ammonium salts of the invention



R_2	N <
CH_3	
$i\text{-}C_3H_7$	$N(C_2H_5)_3$
C_4H_9	
C_2H_5	
C_2H_5	
C_2H_5	$N(C_2H_5)_3$
C_2H_5	

EXAMPLE 26

Ointment

Compound of formula (I), e.g. chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate or chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate	0.2% w/w
Liquid paraffin	10.0% w/w
White soft paraffin	89.8% w/w

Aphthous Ulcer Pellet

Compound of formula (I), as above	0.25 mg
Lactose	69.90 mg
Acacia	3.00 mg
Magnesium stearate	0.75 mg

Retention Enema

Compound of formula (I), as above	0.001% w/v
Tween 80	0.05% w/v
Ethanol	0.015% w/v
Propylparaben	0.02% w/v
Methylparaben	0.08% w/v
Distilled water	q.s. 100 volumes

Eye Drops

Compound of formula (I), as above	0.1% w/v
Tween 80	2.5% w/v
Ethanol	0.75% w/v
Benzalkonium chloride	0.02% w/v
Phenyl ethanol	0.25% w/v
Sodium chloride	0.60% w/v
Water for injection	q.s. 100 volumes

Cl

EXAMPLE 27

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Ointment

Compound of formula (I), e.g. chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate or chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	0.025% w/w
Liquid paraffin	10.175% w/w
White soft paraffin	89.8% w/w

Aphthous Ulcer Pellet

Compound of formula (I), e.g. chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate or chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	0.1 mg
Lactose	69.90 mg
Acacia	3.00 mg
Magnesium stearate	0.75 mg

Retention Enema

Compound of formula (I), e.g. chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androsta-1,4-dien-3-one-17β-carboxylate or chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate	0.001% w/v
Tween 80	0.05% w/v
Ethanol	0.015% w/v
Propylparaben	0.02% w/v
Methylparaben	0.08% w/v
Distilled water	q.s. 100 volumes

Eye Drops

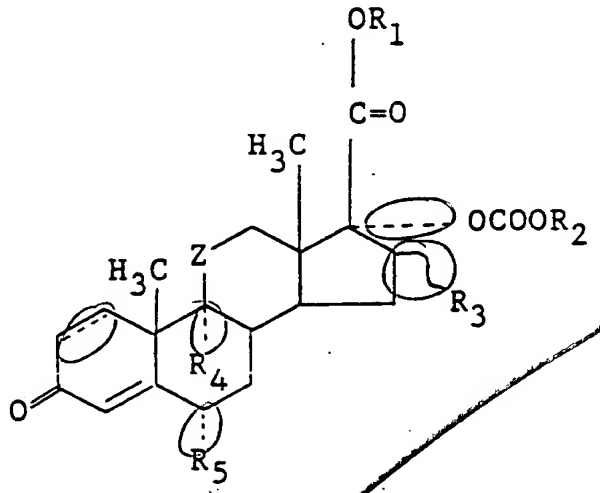
Compound of formula (I), e.g. chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxy-carbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate or chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxy-carbonyloxy-16α-methyl-androsta-1,4-dien-3-one-17β-carboxylate	0.025% w/v
Tween 80	2.5% w/v
Ethanol	0.75% w/v
Benzalkonium chloride	0.02% w/v
Phenyl ethanol	0.25% w/v
Sodium chloride	0.60% w/v
Water for injection	q.s. 100 volumes

Example 28

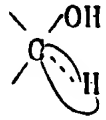
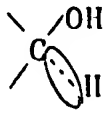
To a solution of 3 grams of chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate in 100 ml of acetonitrile, 7.9 grams of AgF (a 10:1 molar ratio of AgF to steroid) are added, and the mixture is stirred at room temperature for 12 days while shading the reaction system from light. Thereafter, the reaction mixture is filtered, and the solid on the filter is fully washed with ethyl acetate. The filtrate and the ethyl acetate solution are combined, and the mixture is washed with water and a saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The solvents are distilled off, giving 2 grams of crude crystalline product. The product is subjected to preparative thin-layer chromatography (Silica Gel 60F254, Merck), using a mixture of chloroform and methanol (15:1) as an eluting solvent. Then the product is recrystallized from a mixture of tetrahydrofuran and n-hexane to give 180 mg of fluoromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate as colorless needles, melting at 207.5-210°C.

Example 29

Following the general procedure of Example 28 and substituting therein the appropriate reactants affords the following compounds:



T. 1210

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ	mp
29-1	$-CH_2F$	$-C_2H_5$	α-CH_3	F	H		1,4	239-240.5°C (THF/hexane)
29-2	$-CH_2F$	$-CH_2CH_2CH_3$	α-CH_3	F	H		1,4	165-165.5°C (THF/hexane)

The foregoing compounds can be named as follows:

29-1: fluoromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

29-2: fluoromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

From the foregoing description, one of ordinary skill in the art can readily ascertain the essential characteristics of the present invention and, without departing from the spirit and scope thereof, can make various changes in and/or modifications of the invention to adapt it to various usages and conditions. As such, these changes and/or modifications are properly, equitably and intended to be within the full range of equivalence of the following claims.